HISTOPATHOLOGY OF THE SKIN

WALTER F. LEVER, M.D.

Clinical Associate in Dermatology, Harvard Medical School; Assistant Dermatologist, Massachusetts General Hospital; Associate in Dermatology, Peter Bent Brigham Hospital; Consulting Dermatologist, Massachusetts Eye and Ear Infirmary, The Children's Hospital and Robert Breck Brigham Hospital

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In Memory of My Father

DR ALEXANDER LEVER

1877–1916

My First Teacher in Dermatology

Preface to the Second Edition

Descriptive histopathology is regarded by some as a static science in which nowadays but few concepts change But this is not so Many advances have been made in the field of dermatopathology in only the five years that have passed since the appearance of the First Edition of this book Consequently many changes were necessary for this Second Edition

Important advances have been made in recent years in the histologic diagnosis of the vesicular and the bullous diseases especially of pemphigus Therefore the descriptions of these diseases have been entirely rewritten and brought together into a new separate chapter Because of changes in the concept of the histogenesis of the nevus cell the chapter on nevi and melanomas also has been rewritten The use of the periodic acid Schiff reaction for the demonstration of fungi in tissue is an important advance which is taken due notice of in the chapter on fungus diseases Extensive changes also have been made for instance in the descriptions of kraurosis vulvae the purpuras and verruca Furthermore discussion of the following diseases has been incorporated because recent work has increased the interest of dermatologists in them beryllium granuloma papular myxedema porphyria ochronosis hibernoma and hemangiopericytoma Many changes have been made in the Bibliographies that follow each chapter in order to keep them up to date Fifty six new photomicrographs have been added and 14 of the old photomicrographs have been replaced by better ones

It is with great regret that I record the death of Dr Tracy B Mallory former chief of the Pathology Laboratory at the Massachusetts General Hospital To him I owe a great debt of gratitude Dr Benjamin Castleman the present chief of the laboratory has advised and helped me in many ways and I thank him I also wish to express my thanks to Mr Richard W St Clair for producing with great skill the new photomicrographs and to Mr Walter Kahoe Director of the Medical Department of J B Lippincott Company for his many courtesies and his unfailing co-operation

WALTER F LEVER

Preface to the First Edition

This book is based on the courses of dermatopathology which I have been giving in recent years to graduate students of dermatology enrolled at Harvard Medical School and Massachusetts General Hospital The book is written primarily for dermatologists I hope however that it may be useful also to pathologists since dermatopathology is given little consideration in most textbooks of pathology

I have attempted to keep this book short Emphasis has been placed on the essential histologic features Minor details and rare aberrations from the typical histologic picture have been omitted I have allotted more space to the cutaneous diseases in which histologic examination is of diagnostic value than to those in which the histologic picture is not characteristic In spite of my striving for brevity I have discussed the histogenesis of several dermatoses because knowledge of the histogenesis often is of great value for the understanding of the pathologic process

Primarily for the benefit of pathologists who usually are not too familiar with dermatologic diseases I have preceded the histologic discussion of each disease with a short description of the clinical features

A fairly extensive bibliography has been supplied for readers who are interested in obtaining additional information In the selection of articles for the bibliography preference has been given whenever possible to those written in English

I wish to express my deep gratitude to Dr Tracy B Mallory and Dr Benjamin Castleman of the Pathology Laboratory at the Massachusetts General Hospital for the training in pathology they have given me It has been invaluable to me Their teaching is reflected in this book Furthermore I wish to thank Mr Richard W St Clair who with great skill and patience produced all the photomicrographs in this book

WALTER F LEVER

Contents

1

Introduction

TECHNIC FOR BIOPSY

It is important to select a proper site for biopsy In most instances histologic examination of a fully developed lesion will give more information than examination of an early or an involuting lesion An exception to this rule represents vesicular, bullous and pustular lesions For their histologic examination a very early lesion is required otherwise, secondary changes (such as regeneration degeneration or secondary infection) may obscure essential features and make recognition of their mode of formation impossible Generally, it is inadvisable to include normal tissue in the biopsy specimen unless a large specimen is taken or the physician personally supervises the processing of the specimen because improper sectioning by the technician may result in only normal skin being seen in the section The specimen should include subcutaneous fat, because, in many dermatoses characteristic histologic features are found in the lower dermis or in the subcutaneous fat If several types of lesions are present and the diagnosis hinges on the histologic findings much time may be saved by taking specimens for biopsy from more than one lesion

In the author s experience a specimen obtained with a 6 mm biopsy punch nearly always has proved adequate for histologic study Two sutures are sufficient to close the wound

Before placing the specimen in the routine fixative, which in many hospitals is Zenker s or Helly s solution one should consider which stains are desirable Some of the special stains can be performed only if the specimen has been fixed in the appropriate fixative A tabulation of staining methods with the required fixatives is found in Table 1 *on page 29*

LIMITATIONS OF HISTOLOGIC DIAGNOSIS

Although histologic study is one of the most valuable means of diagnosis in dermatology it has its limitations Often no definitive diagnosis can be made The reason for this is that few dermatoses, aside from the tumors, are associated regularly with a diagnostic his

1

Introduction

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2

Embryology of the Skin

THE EPIDERMIS

In the earliest period of fetal life the epidermis consists of a single layer of cells. Between the fifth and the seventh weeks of fetal life this becomes a double layer consisting of an inner layer, the stratum

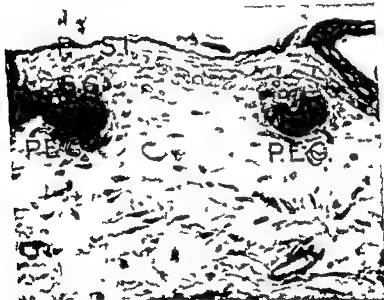


FIG. 1. The skin of an embryo 4 months old. The epidermis consists of three layers: the stratum germinativum (S.G.), the stratum intermedium (S.I.) and the periderm (P.). Two primary epithelial germs (P.E.G.) are shown. The fetal dermis shows many more fibroblasts than the adult dermis. (×400)

germinativum or palisade layer, and an outside layer, the periderm or epitrichial layer. The stratum germinativum is composed of large cuboidal cells, while the periderm consists of flat cells. In the third month single cells appear between the two layers and later form a complete line, the stratum intermedium (Fig. 1). The cells of the

tologic picture Instead, the histologic features may be merely suggestive of a diagnosis or may be entirely nonspecific Even in the case of tumors, difficulties in diagnosis may arise For instance, distinction of squamous cell carcinoma from pseudo epitheliomatous hyperplasia is not always possible In cases of infectious granulomas such as syphilis, tuberculosis and the deep mycoses, a specific diagnosis often cannot be made unless the causative organism can be demonstrated Great difficulties may also be encountered in the histologic study of the large group of noninfectious inflammatory dermatoses In the diseases of this group, such as psoriasis lichen planus and lupus erythematosus in which the histologic picture is diagnostic as a rule *sometimes it may be merely suggestive In other diseases of this group,* such as the various types of dermatitis or eczema the histologic picture *is at best, only suggestive In still others, such as pityriasis rosea* and parapsoriasis it is always nonspecific

Nevertheless frequently, when the histologic picture is not diagnostic, a correlation of the histologic with the clinical findings will make a diagnosis possible

In many instances the chief value of histopathologic study lies in corroborating the clinical diagnosis or in ruling out possible diseases which are being considered on the basis of clinical appearance It is obvious that the histopathologist can give the clinician a maximum amount of information only if every specimen submitted for histologic diagnosis is accompanied by detailed clinical information, including a differential diagnosis

except in a few areas where they persist (See "The Apocrine Glands" page 16)

Melanocytes (Dendritic or Clear Cells) Whereas in the past the melanin producing dendritic or clear cells were considered to be modified basal cells there is now almost complete agreement that they are neural cells which originate in the neural crest and migrate from there with the nerves to the epidermis during early fetal life (DuShane Rawles) Although this origin of the melanocytes has not been proved experimentally in man it has been proved in mice by Rawles who transplanted tissue from the neural crest of mouse embryos to the coelom of albino chicken embryos and observed the development of pigmented melanocytes

In human embryos argentaffine melanocytes first are identified within the epidermis early in the third month They possess long branching dendritic processes which in subsequent months become more numerous and longer up to 100 microns in length joining neighboring melanocytes (Zimmermann and Cornbleet) (For a further discussion of the melanocytes see pages 9 12)

THE DERMIS

The dermis is of mesodermal origin During the first months of fetal life it consists of closely packed spindle shaped cells (mesenchymal cells) During the third month fibrils appear at first as a delicate anastomosing argyrophilic network (reticulum fibers) As the fibers increase in number and thickness they arrange themselves in bundles which no longer can be impregnated with silver and which instead begin to stain with the methods for collagenous fibers (Maximow and Bloom) Simultaneously the mesenchymal cells develop into fibroblasts The elastic fibers appear much later than the collagenous fibers usually in the sixth month (Lynch) The subcutaneous fat first becomes apparent in the third month

It is not as yet settled whether collagen and elastin develop intracellularly by a direct transformation of living substance of mesenchymal cells or extracellularly by precipitation of the ground substance under the influence of an enzyme derived from mesenchymal cells Observations on the development of fibers in tissue cultures favor the theory of their extracellular origin (Maximow and Bloom)

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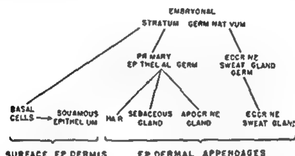
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stratum intermedium are large and because of their clear cytoplasm have a ballooned appearance

At about the fourth month the *periderm separates* to aid in the formation of the vernix caseosa At the same time the stratum intermedium becomes multilayered and develops into the squamous cell layer or stratum malpighii Intercellular bridges become recognizable only after the epidermis has become stratified with several layers

The embryonal stratum germinativum differentiates into the following types of cells (1) the basal cells (2) the eccrine sweat gland germ cells and (3) the primary epithelial germ cells (Chart 1)

CHART 1 —EMBRYOLOGY OF THE EPIDERMIS



Basal Cells While the cells of the embryonal stratum germinativum possess no intercellular bridges the mature basal cells do By progressive differentiation the basal cells develop into squamous cells granular cells and horny cells thus forming the multilayered surface epidermis

Epidermal Appendages The epidermal appendages develop from the primary epithelial germ cells and the eccrine sweat gland germ cells These cells possess no intercellular bridges and form cells without intercellular bridges Primary epithelial germs first appear in the third month of fetal life as epithelial buds projecting into the dermis (*Fig* 1) *Eccrine sweat gland germs* are *first observed in* the fifth or the sixth month

[illegible] glands [illegible] atrix [illegible] nd its the sebaceo[illegible] two inner sheaths (the Huxley and the Henle layers) develop from the hair matrix *The outer sheath of the hair and the ducts of the* sebaceous glands which are composed of prickle cells originate from cells with the potentiality *of forming prickle cells namely from basal* cells (Lever) The apocrine glands which begin to form with the hair and the sebaceous gland involute *before they reach full development*

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3

Histology of the Skin

THE EPIDERMIS

In histologic sections of normal skin, the border between the epidermis and the dermis is irregular because of the fact that numerous cone shaped dermal papillae reach upward and indent the inner surface of the epidermis The ridges of epidermis separating the papillae appear in histologic sections as pegs, and, therefore, often are referred to as rete pegs although the term rete ridges is preferable

Layers of the Epidermis. The epidermis may be divided into four layers (1) the ba

located

THE BASAL LAYER Two types of cells occur in the basal layer basal cells and melanocytes

Basal cells are columnar in shape and lie with their long axis vertical to the dividing line between the epidermis and the dermis They have a deeply basophilic cytoplasm and a darkly staining oval or elongated nucleus. In sections stained with routine stains, the basal cells seem to contain melanin granules often concentrated

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conclusion that the melanin granules were entirely within melanocytes and that the basal cell

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Layers of the Epidermis The epidermis may be divided into four layers

layer as

lucidum

located between the granular and the horny layers The cells in the various layers represent different stages in the gradual evolution of the basal cell into cornified cells and do not represent different types of cells

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epidermis to the dermis is accomplished by the firm interlocking of cytoplasmic processes of the basal cells with reticulum fibers located in the uppermost dermis Whereas,

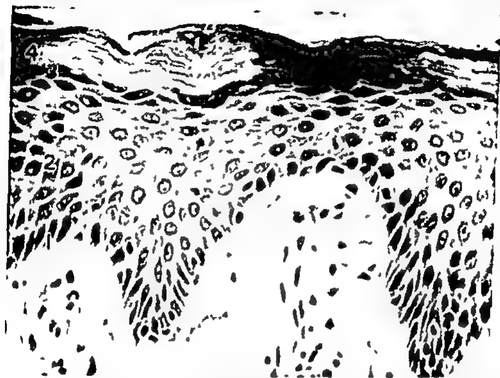


FIG 2 Normal epidermis, dorsum of the hand Four layers can be recognized (1) basal layer (2) stratum malpighii (3) granular layer and (4) horny layer No stratum lucidum is present Note the presence of intercellular bridges between the basal cells Several clear cells (melanocytes) are present in the basal layer They possess a small dark nucleus and clear cytoplasm (×400)

in perpendicular sections these reticulum fibers appear like the bristles of a brush (Fig 3), horizontal sections reveal them to form a continuous fibrillar meshwork around the cytoplasmic processes of the basal cells (Odland) In contrast with formerly expressed views, elastic fibers do not contribute to the coherence of the dermis and the epidermis since they do not extend high enough to reach the epidermis (Dick)

Whereas routine stains do not show a basement membrane, stains with the periodic acid Schiff stain after Hotchkiss and McManus (see page 30) show a thin homogeneous dense band (Fig 4) at the dermal epidermal junction, indicating the presence of a relatively large amount of polysaccharide material in this zone (Stoughton and

Wells) This band represents a relative barrier to the diffusion of large particles as proved by the fact that dye injected intradermally beneath a subepidermal bulla will not appear in the bulla fluid al



FIG 3 (*Top*) ... for reticulum fi... work into which ... in a firm attachi...

FIG 4 (*Bottom*) Junction between the epiderm...

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Melanocytes (Clear or Dendritic Cells) Melanocytes are of neural origin (see Embryology page 5) They stain with Bloch s dopa

stain (because they have the ability to form melanin) and usually also with silver stains (*because they contain melanin*) (see page 12) They also stain with gold In sections stained with hematoxylin and eosin *melanocytes appear as clear cells having a small* dark staining nucleus and a clear, slightly basophilic cytoplasm (Figs 2 and 254) On the other hand, *in sections impregnated with silver* they appear as dendritic cells with numerous long, branching processes provided a sufficient amount of melanin granules are present within the processes to show their outline (Ebert, Becker Jr, Fitzpatrick and Montgomery)

The Stratum Malpighii The cells of the stratum malpighii which are called squamous cells or prickle cells, are polygonal and form a mosaic They become flattened toward the surface (Fig 2) The cells are separated by spaces which are traversed by intercellular bridges or prickles They separate the squamous cells so that lymphatic fluid can circulate around them and supply them with nourishment The intercellular bridges are formed by the cytoplasm of adjoining cells and tonofibrils which extend through them from cell to cell As studies by phase contrast and polarization microscopy have shown, tonofibrils pass uninterruptedly from one cell to another all the way from the basal cell layer to the stratum corneum Roentgen spectography suggests that the tonofibrils consist of keratin (Nelemans Keuning van Rijssel and Ruiter)

Each of the intercellular bridges in the stratum malpighii contains a small nodular thickening called the nodule of Bizzozero These nodules are stained selectively by Heidenhain s iron hematoxylin which does not stain the epidermal cells and bridges (Tavre) This special staining reaction suggests that the nodules of Bizzozero are special structures and not just a thickening of the intercellular bridges Nieuwmeijer on the other hand believes that they merely represent an optical effect produced by the crossing of tonofibrils in the intercellular bridges

If a gold stain is employed one may observe interspersed between the cells of the stratum malpighii gold impregnated cells with den
[illegible] not observed

so far about their nature Masson regards them as worn out [illegible] cytes which are being carried away passively toward the surface Ferreira Marques points out that schwannian cells generally are auro
[illegible]

[illegible]
represent intra epidermal receptors of pain Becker Jr [illegible] and Montgomery, on the other hand regard the Langerhans cells as ordinary melanocytes and maintain that they appear to lie in the

superficial epidermis only because of distortion and wrinkling of the tissue produced by the acid used in the gold impregnation In separated epidermis, which is less distorted by acid than whole skin, they found gold impregnated cells only at the junction of the epidermis and the dermis and never in the upper layers of the epidermis

THE GRANULAR LAYER The cells of the granular layer are diamond shaped and filled with granules (Fig 2). The granules are

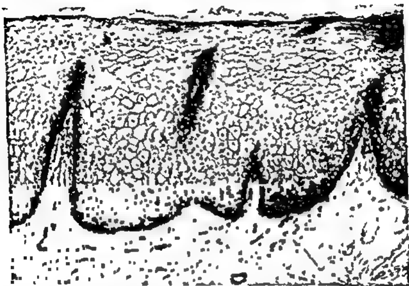


FIG 5 Epithelium of the oral mucosa. No keratin is formed The epithelial cells in their migration from the basal layer to the surface first become vacuolated then shrink and finally desquamate (×200)

coarse, irregular in size and shape, and strongly light refractile The chemical nature of the granules is not known Unna called them keratohyaline granules, but the substance differs in its chemical behavior from both keratin and hyalin The thickness of this layer

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this layer varies from 0 02 mm on the flexor surface of the forearm to 0 5 mm and more on the soles

cells; they are closely

are present in this lay

The mucous membrane of the mouth normally possesses no gran

ular cells and no horny layer There the epithelial cells in their migration from the basal layer to the surface first become vacuolated, then shrink and finally desquamate (Fig 5)

THE STRATUM LUCIDUM This layer occurs only on the palms and the soles It is located above the granular layer and is composed of two or three layers of flat, anuclear cells of homogeneous, transparent appearance The substance filling the cells and giving them the oily appearance is called eleidin, which is believed to be formed by lique faction of the keratohyaline granules Ordinarily, this layer cannot be demonstrated in sections stained by routine staining methods However, it can be shown by two rather complicated staining methods described by MacLeod and Muende

Pigment of the Epidermis For the study of cutaneous pigmenta tion, two stains are necessary the silver stain and the dopa stain Silver stains melanin black, thus indicating its presence Dopa stains

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Becker, Praver and Thatcher, consists in bathing sections of skin in a 0 1 per cent solution of levorotatory 3,4 dihydroxyphenylalanine (called "dopa" for short) Following Bloch's suggestion, the cells that stain dark with the dopa stain are called dopa positive Such cells stain dark because the enzyme tyrosinase which they contain changes the colorless dopa of the stain into a dark insoluble product, the dopa melanin (Bloch, 1927) The dopa stain closely imitates physio logic melanin formation, which occurs because the amino acid tyro sine in cells containing the enzyme tyrosinase is transformed to dopa and further to melanin by the action of this enzyme (Lerner and Fitzpatrick)

The dopa stain shows that in the basal layer only the neural

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layer of the epidermis but also are found interspersed between the hair matrix cells of the hair bulb When active melanin formation occurs (e g , after exposure to the sun) the number of dopa positive melanocytes in the basal layer of the epidermis increases greatly

The silver stain does not, like the dopa stain, demonstrate the site of formation of melanin but instead demonstrates the presence of melanin Thus, in the

also mesodermal phag

matophores stain pos

dermis melanin is seen only in the region of the basal layer However in a deeply pigmented skin as in the Negro, melanin is found also in the upper layers of the epidermis and in phagocytic cells of the dermis Studies by Becker Jr Fitzpatrick and Montgomery on separated epidermis have revealed that even in deeply pigmented skin melanin is never found in basal cells or squamous cells It is contained exclusively in melanocytes and their dendritic processes until the stratum granulosum is reached At this level the dendrites terminate and free melanin granules are seen in the granular layer and the stratum corneum

The Nerves of the ...

... intraepidermal terminal nerve fibers mediating pain have been demonstrated extending upward from the dermis into the lower layers of the stratum malpighii and in the fingers even into the stratum granulosum (Woollard Weddell and Harpman) With the methylene blue method these nerve fibers subserving pain have ...

low ...

ture ... receptors of touch They are most abundant on the fingers where they may show connections by means of medullated fibers with Meissner s tactile corpuscles located in the papillae (Woollard)

Formerly two types of cells within the epidermis were regarded as nerve end cells the Merkel Ranvier tactile cells and the Langerhans cells The Merkel Ranvier cell is identical with the clear cell and as such is a mela...

THE EPIDERMAL APPENDAGES

The Sweat or Eccrine Glands Sweat glands are present everywhere in the human skin They are found in greatest abundance on the palms and the soles and in the axillae They are tubular glands whose secretory cells during the process of secretion do not change in size or shape and do not release any cellular material into the lumen of the gland Schiefferdecker called the sweat glands eccrine glands because of his belief that their secretory cells ...

Sweat glands are composed ... The secretory portion lies coiled ... in the derm... and ... ermis ... fatty

tissue which connects with the subcutaneous fat. Although eccrine glands are formed embryologically with two layers of epithelial cells throughout, only one distinct layer, composed of secretory cells, lines



FIG. 6 Normal skin, back of neck. On the left side of the illustration, a sweat duct (S.D.) enters the epidermis. In the center, a large sebaceous gland (S.G.) leads into a follicle containing a lanugo hair. On the right side, a large hair (H.) lies within a follicle surrounded by sebaceous glands. An arrector pili muscle (A.P.) is situated in the obtuse angle of the hair. Beneath the large sebaceous gland, a coiled up eccrine sweat gland (S.W.G.) is present. (×50)

the secretory portion in postembryonal life (Fig. 7), because the second, outer layer of epithelial cells has become differentiated into myoepithelial cells. The secretory cells are large, cylindrical cells with clear, slightly basophilic cytoplasm. The myoepithelial cells are small, spindle-shaped cells inserted sporadically between the secretory cells at their bases. Their long axis extends at a right angle to that of the secretory cells, i.e., parallel with the circumference of the

gland They possess long processes composed of cytoplasmic fibrils with the same staining properties as smooth muscle and are con tractile By their contraction they drive the secretion out of the secretory cells into the lumen Peripheral to the myo epithelial cells lies a thin hyaline basement membrane



E — myo-epithelial cells are wedged in at their bases (M C) The ducts are composed of two layers of small cuboidal dark staining cells The lumina of the ducts are lined with a homogeneous cuticle (×400)

The ductal part of the sweat glands leads into the epidermis (Fig 6) Up to the epidermis the duct is composed of two layers of small cuboidal deeply basophilic epithelial cells No peripheral basement membrane is present but the lumen of the duct is lined with a deeply eosinophilic homogeneous membrane or cuticle Some authors state that the d … dermis a… cells in … yardy and Memmesheimer, 1936) Others however like Pinkus maintain that sweat ducts have their own lining cells within the epidermis The observation by Holyoke and Lobitz that the cells lining the intra epidermal portion of the

sweat duct maintain their normal structure when surrounded by carcinoma tends to support Pinkus' contention.

The lumen of sweat glands is small, measuring approximately 20 microns in diameter in the secretory portion, and less still in the ductal portion. In the horny layer of the epidermis, it measures only from 5 to 10 microns in diameter. (The diameter of an erythrocyte is 7.6 microns.)

The Apocrine Glands. The apocrine glands differ from the eccrine glands in origin, distribution, mode of secretion, size and staining reactions. They represent vestigial scent glands.



FIG 8 Apocrine glands and eccrine sweat glands in the axilla. Note the great difference in the size of the lumina of the apocrine glands (*left*), and of the eccrine glands (*right*) The apocrine gland cells show "decapitation secretion (×100)

[illegible] glands

[illegible]

directly to the epidermis

Apocrine glands are encountered in only a few areas in the axillae, around the nipples, in the perigenital and the perianal regions, and, [illegible] fied glands in the external ear canal (ceruminous glands), in [illegible] ie breast (mammary glands) Oc- [illegible] found on the abdomen and the chest.

name apocrine for these glands because part of the cytoplasm of their secretory cells is pushed off (apo = off)

because the outer layer has become differentiated just as in the sweat glands into myo epithelial cells The secretory cells vary greatly in height depending on the stage of their secretory cycle. The secretory cells stain distinctly eosinophilic in contrast with the secretory cells of sweat glands which stain slightly basophilic In addition they frequently contain granules which react positively to iron stains (Homma) The lumen of the apocrine glands is filled with cellular

on the modified skin of the vermilion border of the lips the glans penis the inner surface of the prepuce the labia minora and the

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duct

a hair On modified skin where hair is absent, sebaceous glands lead into follicles devoid of hair The meibomian glands of the eyelids are

...scopic exam

ination when the disks are crossed (see page 31)

Hair. The hair consists of the hair shaft, composed of keratinized cells, and the hair root, composed of nonkeratinized cells. The hair root terminates in a knoblike expansion, the hair bulb, containing the hair matrix cells. A small connective tissue structure, the papilla,

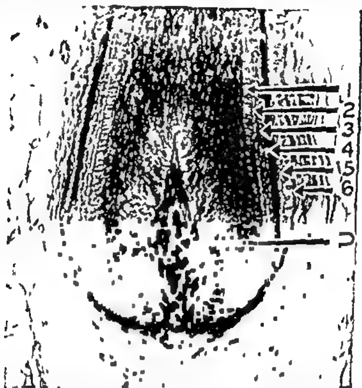


Fig. 9 Lower part of a hair. The hair papilla (P) composed of connective tissue, protrudes into the hair bulb. The various linings of the hair can be recognized. They are, from the inside to the outside (1) the hair cuticle, (2) the sheath cuticle, (3) the Huxley layer, (4) the Henle layer (which stains darkly) (5) the outer hair sheath and (6) the vitreous layer (×200)

protrudes into the hair bulb (Fig. 9). The papilla is richly supplied with blood vessels and nerves and, in individuals with dark hair, contains considerable amounts of melanin situated largely in macrophages.

Each hair is surrounded by two inner sheaths and an outer sheath all composed of epithelial cells. The two inner sheaths develop, together with the hair, from hair matrix cells, while the outer sheath represents a downward extension of the epidermis.

The hair root consists of a *medulla* and a *cortex*. Its cells possess large, vesicular nuclei and contain variable amounts of melanin. Dopa positive melanocytes are interspersed between the hair cells

where the hair rests on the papilla Peripheral to the cortex is the hair cuticle which is composed of a single row of nucleated cells (Fig 9 ,)

The hair shaft is composed of fully keratinized cells closely united with one another and containing either no nuclei or elongated greatly shrunken nuclei No medulla and no hair cuticle are recognizable since they have lost their identity in the process of keratinization It may be pointed out that keratinization in the hair proceeds without the interposition of granular cells

The two inner hair sheaths accompany the hair to approximately the level at which keratinization begins They are separated from the hair cuticle by the sheath cuticle (Fig 9 .) The sheath cuticle consists of a single layer of c

the cells of the hair cuticle

granules The Henle layer co
stain darkly because they ar
granules On th s account tl
some authors have even stated that the Henle layer contained no nuclei However they can be recognized easily in hair cut on a diagonal plane

The
ward t
the ep
bulb Its cells have a clear vacuolated appearance due to the presence of considerable amounts of glycogen in the cytoplasm Outside of the outer hair sheath lies a thin membrane of condensed connective tissue the glassy or vitreous layer (Fig 9,)

Nails. The nail is composed of keratin It grows from the nail matrix which is located beneath the nail fold The nail matrix consists of epidermis without a stratum granulosum Thus just as in the hair keratinization in the nail proceeds without the interposition of a granular layer The epithelium of the nail bed has no stratum granulosum either Its rete ridges are oriented not as a network of anastomosing ridges as elsewhere in the skin but as parallel longitudinal ridges

THE DERMIS

Three types of fibers occur in the dermis collagenous elastic and reticulum fibers.

Collagenous Fibers Collagen forms more than 98 per cent of the connective tissue of the dermis It occurs in bundles of fibers held

Hair. The hair consists of the hair shaft, composed of keratinized cells, and the hair root, composed of nonkeratinized cells The hair root terminates in a knoblike expansion, the hair bulb, containing the hair matrix cells A small connective tissue structure, the papilla,

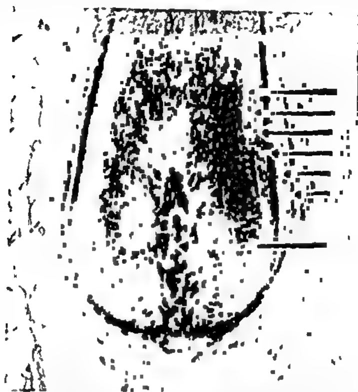


Fig 9 Lower part of a hair. The hair papilla (P) composed of connective tissue, protrudes into the hair bulb The various linings of the hair can be recognized They are, from the inside to the outside (1) the hair cuticle, (2) the sheath cuticle (3) the Huxley layer (4) the Henle layer (which stains darkly) (5) the outer hair sheath and (6) the vitreous layer (×200)

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Each hair is surrounded by two inner sheaths and an outer sheath, all composed of epithelial cells The two inner sheaths develop, together with the hair, from hair matrix cells, while the outer sheath represents a downward extension of the epidermis

The hair root consists of a medulla and a cortex Its cells possess, large, vesicular nuclei and contain variable amounts of melanin Dopa positive melanocytes are interspersed between the hair cells

are penetrated more easily by the colloidal silver (Nageotte and Guyon).

namely, reticulum cells, histiocytes, lymphocytes, vascular endothelial cells, smooth as well as striated muscle cells and fat cells (Dublin).

of sweat glands and around the blood vessels In addition, reticulum fibers are present in the uppermost dermis (Fig 3) In perpendicular sections, these reticulum fibers appear arranged like the bristles of a brush, but horizontal sections show a continuous fibrillar mesh work (Odland) Due to the fact that cytoplasmic processes of the basal cells extend ... he

... is

the abundance of reticulum fibers in pathologic conditions in which there is formation of young mesodermal cells Large amounts of reticulum fibers are presen...

... have become condensed to collagen

Nerves and Nerve End Organs On sections stained by routine methods, one easily can recognize the large nerves and the Pacini and Meissner end organs The fine nerves and the other nerve end organs require special staining either impregnation with silver salts, e g by the Bodian stain (Bodian), or *vital staining* with methylene blue (Woollard, Weddell and Harpman)

The skin is endowed with nerves from both the cerebrospinal and the autonomic or vegetative, system The sensory nerves belong to the cerebrospinal system, while the vasomotor nerves and the nerves supplying the smooth muscles and the sweat gland ...

... be differentiated to a certain degree, since the former up to their terminal ramifications always possess a myelin sheath while the latter usually do not. A few sympathetic fibers may possess a myelin sheath (Jaeger)

together by an interfibrillary ground substance. The fibers and the bundles are coarsest toward the subcutaneous tissue and finest toward the outermost portion of the dermis. In the papillary and the subpapillary portions of the dermis, the collagen bundles run in an apparently haphazard manner and do not interlace. In the lower dermis, the bundles are arranged nearly parallel to the surface of the skin and do interlace. Collagen bundles are only slightly extensible, but, since they are wavy, they permit stretching of the skin. A small number of cells, the fibroblasts, are interspersed between the collagen bundles. They have oval or spindle shaped, pale nuclei en do [illegible] embrane (see page 36)

[illegible] bundles are interwoven with a web of [illegible] rs are slightly wavy, and, therefore, only a small portion of any fiber is seen in any histologic section. The fibers are thickest and densest in the lower portion of the dermis, where they are arranged just as the collagen bundles, chiefly parallel to the surface of the skin and are up to 200 microns long. In the uppermost dermis, there are only few small fibers running horizontally, obliquely and sometimes vertically. From these fibers still finer fibrils spread out toward the epidermis but do not reach it (Dick). Therefore, elastic fibers do not contribute to the attachment of the epidermis to the dermis, as had been believed formerly. [illegible]

turn of the skin into its normal position after stretching, thus supplying elasticity to the skin. Their rigidity prevents overdistention. When the skin is overstretched, as in pregnancy, the elastic fibers may break and degenerate.

Reticulum Fibers. Reticulum fibers (or lattice fibers, "Gitterfasern") form a third system of fibers. They are not visible as such with routine stains but stain with silver (Foot's stain). It now is agreed quite generally that [illegible] collagen"), or collagen occu [illegible] lagen is merely compacted [illegible] easily can see, in sections containing reticulum fibers and stained with Foot's stain, that in areas where the reticulum fibers are densest they tend to aggregate into collagen bundles (Fig. 89). The essential identity of collagen and reticulum is based on the fact that both react alike to all stains with the exception of silver stains (Mallory and Parker). The difference in argyrophilic properties is due to the fact that reticulum fibrils are finer than collagen fibrils and therefore

detected easily in microscopic sections (Fig 10) Located in the subcutis especially of the palms and the soles they aid in the mediation of the sense of pressure They are large oval onionlike structures composed of a cortex a core and a myelinated nerve which enters the structure at its lower pole The cortex consists of from 20 to 60 concentric layers of fibrous tissue the core consists of semisolid material in which the nerve is embedded The myelin sheath accompanies the nerve up to the upper pole of the Pacini corpuscle There the nerve ends in numerous ramifications

MEISSNER TACTILE BODIES These are located in papillae (Fig 11) and mediate a sense of touch They are present almost exclusively on the hands and the feet and are especially numerous on the palmar surfaces of the fingers with their number increasing distally On the finger tips they lie in groups of two or three in adjoining papillae thus supplying a spatial relationship to the sense of touch (Weddell) They are cone shaped and lie with their long axis perpendicular to the surface of the skin They are of such size that they occupy the greater part of the papilla in which they are located They are composed of a connective tissue capsule and flattened cells probably schwannian cells which have their longest diameter in a transverse direction One to four myelinated nerves lead to each body They lose their myelin sheath on entering the body and divide into fibrils which pass upward in a spiral fashion



FIG 11 A Meissner tactile body located in a papilla of the fingertip It is composed of flattened (schwannian) cells which have their longest diameter in a transverse *direction* Since this is a hematoxylin and eosin stain the nerve fibrils cannot be visualized (X400)

RUFFINI BODIES The Ruffini bodies are located in the deeper dermis and in the subcutis Some believe that they mediate a sensation of heat They present brushlike ramifications of a nonmyelinated nerve within a thin connective tissue capsule

KRAUSE BODIES *The krause bodies* are irregularly shaped spherical formations located in the dermis close to the epidermis They

The basic unit of any nerve is the neurofibril, several of which form a neurite or axon. An axon may or may not have a myelin sheath, but always is surrounded, except at its terminal ramifications, by the neuro ectodermal schwannian sheath and the mesodermal endoneurium. In medium-sized nerves, several such units are bound together by the perineurium. Large nerve trunks have several such components and an epineurium as a cover. All autonomic nerves and



Fig 10. Pacini corpuscles in the subcutaneous fat of a fingertip. Their largeness becomes apparent if one compares their size with that of the eccrine sweat glands and their ducts which are located on the right side of the field (×50)

most cerebrospinal nerves end freely in numerous ramifications However, some of the latter end in special nerve end organs.

Nerve end organs are not present to an equal degree everywhere. They abound in areas of refined sensations, such as the palms and the soles, the lips and the genital region, and are sparse elsewhere The function of some is not established clearly. Several types of nerve end organs occur: the Pacini bodies, the Meissner tactile bodies, the Ruffini bodies, the Krause bodies and the genital corpuscles These end organs all have a similar structure a connective-tissue capsule surrounding a core in which the afferent nerve splits up into numerous branches.

Pacini Corpuscles. The Pacini corpuscles are the largest of the end organs They measure up to 2 mm in diameter and thus are

collagen bundles Lymphatic vessels begin as loops in the papillae and lead down to a lymphatic plexus in the subpapillary layer from which they pass down through the dermis to a deeper plexus at the junction of the dermis and the subcutis Lymphatic vessels are lined by only one layer of endothelial cells

pilorum the tunica dartos of the scrotum and the muscle fibers in the areola of the nipple are smooth muscles The muscle fibers of the arrectores pilorum are anchored in the connective tissue of the papillae and are attached to the hair follicles below the sebaceous gland They are situated in the obtuse angle of the follicle, so that on contracting they make the follicle more vertical and produce gooseflesh (Fig 6)

Striated or voluntary muscle shows cross striation of its fibers The nuclei are located at the periphery of the fibers Striated muscle is found in the skin of the neck (platysma) and the face (muscles of expression)

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have a thin fibrous capsule within which nonmyelinated nerves branch They are believed to mediate a sensation of cold

GENITAL CORPUSCLES These have the same general structure as the Krause bodies, but are larger and have a thicker capsule

MERKEL-RANVIER TACTILE CELLS These cells, located in the epidermis, are discussed on page 13

Blood Vessels. The arrangement of the cutaneous blood vessels is inconstant and varies in different parts of the skin Nevertheless a deep plexus at the junction of the dermis and the subcutaneous tissue and a superficial plexus in the subpapillary layer are always present The deep plexus has arterioles which possess three layers adventitia, media and intima The media and the adventitia gradually become thinner as the arteriole ascends through the dermis The capillaries in the papillary layer are composed merely of one layer of endothelial cells surrounded by a few histiocytes (perithelial cells) In some instances, an additional type of cell, called the pericyte, is present This cell has branching processes which encircle the capillary and are contractile They can thus change the caliber of the lumen They represent modified smooth muscle cells (Stout and Murray)

A special structure, the glomus is distributed widely throughout the dermis, but occurs most abundantly on the tips of the fingers and the toes and in the nailbeds The glomus is concerned with temperature regulation and represents a special short circuit device connecting, without the interposition of capillaries, an arteriole with a venule It consists of an arterial and a venous segment The arterial segment, called the Sucquet Hoyer canal, branches from an arteriole and has a narrow lumen and a thick wall The wall consists of an inner endothelial layer and of several layers of glomus cells which are large cells with clear cytoplasm resembling epithelioid cells The glomus cells are in *intimate association with a rich network of non* myelinated nerve fibrils demonstrable by silver stain Although myofibrils are sparse or absent in the glomus cells they are contractile The glomus cell generally has been regarded as a modified smooth muscle cell (Popoff Weidman) On the basis of tissue culture experiments, Murray and Stout believe that the glomus cell is derived from the pericyte The venous segment of the glomus has a wide lumen The blood is emptied from the venous segment *into sub*papillary venules and through the latter into deeper veins

Lymphatic Vessels. Lymphatic fluid circulates *in the epidermis* around the squamous cells, which are kept apart by intercellular bridges or prickles *Similarly, lymphatic fluid circulates* between the

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TABLE 1.—SURVEY OF STAINING METHODS EMPLOYED AT THE MASSACHUSETTS GENERAL HOSPITAL

FIXATION AND EMBEDDING	STAIN	PURPOSE OF STAIN	RESULTS
Helly's—paraffin (Autotechnicon)	Hematoxylin and eosin	Routine	Nuclei blue, collagen, nerves, muscle red
Helly's—paraffin (Autotechnicon)	Phosphotungstic acid hematoxylin	Nuclear details and for distinction of collagen and muscle	Nuclei, nerves, muscle blue, collagen brown
Helly's—paraffin (Autotechnicon)	Aniline blue (Mallory)	Collagen	Nuclei, nerves, muscle bright red, collagen blue
Helly's—paraffin (Autotechnicon)	Masson's trichrome	Collagen	Nuclei, nerves, muscle dark red, collagen green
Helly's—paraffin (Autotechnicon)	Van Gieson	Collagen	Collagen red, nuclei, nerves, muscle yellow
Helly's—paraffin (Autotechnicon)	Verhoeff	Elastic tissue	Elastic tissue black
Helly's—paraffin (Autotechnicon)	Foot	Reticulum	Reticulum and neurofibrils black
Helly's—paraffin (Autotechnicon)	Potassium ferrocyanide	Iron	Iron blue
Helly's—paraffin (Autotechnicon)	Giemsa	Eosinophils, bacteria, Donovan bodies, *Leishmania*, Frisch bacilli, *Histoplasma capsulatum*	Bacteria blue, granules of eosinophils, Donovan bodies, *Leishmania*, Frisch bacilli, *Histoplasma capsulatum* brilliant red
Helly's—paraffin (Autotechnicon)	Gram	Bacteria	Gram positive bacteria blue, Gram-negative bacteria red
Helly's—paraffin (Autotechnicon)	Ziehl Neelsen Fite	Acid fast bacteria	Acid fast bacteria red Acid fast bacteria black
10% Formalin—paraffin	Levaditi	Spirochetes	Spirochetes black
10% Formalin—paraffin	Bodian	Nerves	Neurofibrils black
10% Formalin—paraffin	[illegible]	[illegible]	[illegible]
10% Formalin—frozen section	[illegible]	[illegible]	[illegible] cholesterol brownish red
10% Formalin—frozen section	Crystal violet	Amyloid	Amyloid purple
Absolute alcohol—celloidin	Mucicarmine	Mucin	Mucin red
80% alcohol—paraffin	Von Kossa	Calcium	Calcium black
Fresh tissue—frozen section	Dopa	Melanin producing cells	Melanin producing cells show dark granules

4

Laboratory Methods

FIXATION, EMBEDDING AND STAINING

Fixation. Helly's fixative is used routinely in the Pathology Laboratory of the Massachusetts General Hospital For its preparation two solutions are required (1) Zenker's solution

Potassium dichromate	25 Gm
Mercury bichloride	80 Gm
Water	1000 cc

and (2) Formalin (which is a 40 per cent aqueous solution of formaldehyde) Formalin 1 cc. is added to each 20 cc of Zenker's solution just before use The specimen should remain not less than 5 hours and not longer than 24 hours in Helly's fixative It is then washed in running water for at least 2 hours and transferred into 80 per cent alcohol, in which it can be left indefinitely

For specimens which have to be mailed, the fixative of choice is 10 per cent Formalin because specimens may remain in this fixative indefinitely One cc of Formalin is added to each 9 cc of water just before use

Helly's fixative is contraindicated if one desires to demonstrate lipids, nerve fibers, amyloid, granules of mast cells, spirochetes, calcium or mucin, or if one wishes to perform a dopa stain For the demonstration of lipids, nerve fibers, amyloid, granules of mast cells and spirochetes, fixation in 10 per cent Formalin is required, to demonstrate calcium, 80 per cent alcohol is used, and for demonstration of mucin absolute alcohol is the approved fixative For the dopa stain, no fixative should be employed the fresh tissue should merely be wrapped in moist gauze and sent to the laboratory

Dehydrating and Embedding. Following fixation, all routine specimens are placed successively into several beakers containing dioxane in increasing concentrations for dehydration and several beakers of hot paraffin for embedding This may be done by hand or with the aid of an Autotechnicon machine

In the Pathology Laboratory of the Massachusetts General Hospital as in most other such laboratories all routine specimens,

TABLE 1.—SURVEY OF STAINING METHODS EMPLOYED AT THE MASSACHUSETTS GENERAL HOSPITAL

Fixation and Embedding	Stain	Purpose of Stain	Results
Helly's—paraffin (Autotechnicon)	Hematoxylin and eosin	Routine	Nuclei blue; collagen, nerves, muscle red
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Helly's—paraffin (Autotechnicon)	Aniline blue (Mallory)	Collagen	Nuclei, nerves, muscle bright red; collagen blue
Helly's—paraffin (Autotechnicon)	Masson's trichrome	Collagen	Nuclei, nerves, muscle dark red; collagen green
Helly's—paraffin (Autotechnicon)	Van Gieson	Collagen	Collagen red; nuclei, nerves, muscle yellow
Helly's—paraffin (Autotechnicon)	Verhoeff	Elastic tissue	Elastic tissue black
Helly's—paraffin (Autotechnicon)	Foot	Reticulum	Reticulum and neurofibrils black
H[illegible] paraffin	P[illegible]		
		Leishmania, Frisch bacilli, Histoplasma capsulatum	[illegible] Donovan bodies, Leishmania, Frisch bacilli, H. stoplasma capsulatum brilliant red
Helly's—paraffin (Autotechnicon)	Gram	Bacteria	Gram positive bacteria blue; Gram negative bacteria red
Helly's—paraffin (Autotechnicon)	Ziehl-Neelsen; Fite	Acid fast bacteria	Acid fast bacteria red; Acid fast bacteria black
10% Formalin—paraffin	Levaditi	Spirochetes	Spirochetes black
10% Formalin—paraffin	Bodian	Nerves	Neurofibrils black
10% Formalin—paraffin	Methylene blue; Giemsa	Granules of mast cells	Mast cell granules purple
10% Formalin—frozen section	Scarlet red	Lipids	Neutral fat bright orange; cholesterol brownish red
10% Formalin—frozen section	Crystal violet	Amyloid	Amyloid purple
Absolute alcohol—celloidin	Mucicarmine	Mucin	Mucin red
80% alcohol—paraffin	Von Kossa	Calcium	Calcium black
Fresh tissue—frozen section	Dopa	Melanin producing cells	Melanin producing cells show dark granules

whether unfixed or already placed in Helly's fixative or in 10 per cent Formalin, are sent through the Autotechnicon This machine, which is controlled by an electric clock, accomplishes fixation, dehydration and embedding automatically overnight The specimens are placed in small, perforated cassettes, which are then put into a perforated metal basket suspended from an arm of the machine. The metal basket is automatically lowered into and raised out of a succession of beakers containing Helly's fixative, water, 95 per cent alcohol, dioxane and warm liquid paraffin

Specimens that are to be stained for lipids, nerve fibers, amyloid calcium, mucin, spirochetes or granules of mast cells, or are to be treated with the dopa stain, are not sent through the Autotechnicon, in order to avoid exposure to Helly's fixative Specimens to be stained for nerve fibers calcium, granules of mast cells or spirochetes, after fixation, are carried by hand through dioxane and embedded in paraffin Specimens to be stained for mucin, after fixation are embedded in celloidin Specimens to be stained for lipids or amyloid, after fixation, are cut on the freezing microtome and then stained Specimens to be stained with dopa are cut on the freezing microtome without previous fixation

Staining All routine specimens, after having been cut on a rotary microtome into sections from 5 to 8 microns thick, are stained with hematoxylin and eosin With this method all nuclei stain blue, and collagen, muscle and nerves stain red Special stains are employed for the demonstration of particular structures (see Table 1)

HISTOCHEMICAL STAINING

Brief mention may be made of two histochemical stains which have attained considerable practical importance the Feulgen reaction and the Hotchkiss McManus stain (DeLamater, Mescon and Barger) Both stains can be carried out on material fixed in 10 per cent Formalin

The Feulgen reaction results in red staining of desoxyribonucleic acid (DNA) which is present in nuclei and in many virus inclusion bodies On the other hand, ribonucleic acid (RNA), present in nucleoli, cytoplasm and keratohyalin, does not stain This reaction is important as a stain for viruses since it often allows their differentiation from nucleoli and keratohyaline granules

The Hotchkiss-McManus stain, or periodic acid Schiff (PAS) stain, demonstrates the presence of polysaccharides such as glycogen, hyaluronic acid and other mucoid substances by staining them red It is also of value in the study of fibrinoid degeneration where there is depolymerization of collagen resulting in the formation of polysaccharides For the demonstration of glycogen, it is necessary to

compare two serial sections one exposed to diastase prior to staining and the other not Since the split products of glycogen resulting from the action of the diastase no longer are colored red by this stain only such substances represent glycogen which stain red without preliminary diastase digestion but do not stain after diastase digestion

In addition the Hotchkiss McManus stain is of great value in the demonstration of fungi Since the cell walls of fungi are composed of a mixture of cellulose and chitin they contain considerable amounts of polysaccharides All fungi therefore stain bright red and thus are detected easily in histologic sections because other tissues stain very faintly or not at all (Kligman Mescon and DeLamater)

POLARISCOPIC EXAMINATION

Polariscopic examination is the examination of histologic sections under the microscope with polarized light—i e with light from which all rays except those vibrating in one plane are excluded

For the polariscopic examination two disks made of polarizing plastics are inserted into the microscope One disk is placed below the condenser of the microscope and acts as the polarizer The second disk is placed into the eyepiece of the microscope and acts as the analyzer When the eyepiece containing the analyzing disk is rotated so that the path of the light through the two disks is broken at a right angle the field is dark When however doubly refractile lipids are introduced between the two disks they break the polarization and are visible as bright white bodies *in the dark field*

Cholesterol and cholesterol esters are doubly refractile while neutral fats are not Doubly refractile fats are called anisotropic the others isotropic Doubly refractile lipids are present regularly in the cutaneous lesions of xanthomatosis and hyperlipemia in xanthelasma palpebrarum and in extracellular cholesterosis They are present occasionally in Hand Schuller Christian disease in foreign body granulomas and in histiocytoma The lipid material in lipoid proteinosis and necrobiosis lipoidica diabeticorum however is not doubly refractile as a rule

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5

Morphology of the Mesodermal Cells

Various types of mesodermal cells infiltrate the dermis and occasionally the epidermis in the inflammatory dermatoses, in the granulomas and in the lymphomas It is important for diagnostic purposes to identify the cell types Three groups of mesodermal cells are recognized generally the myeloid group, the lymphoid group and the reticular (or histiocytic) group In addition, plasma cells and mast cells occur It is likely that both originate from the reticular group of cells

MYELOID GROUP

Polymorphonuclear leukocytes and eosinophilic leukocytes may occur in the skin in various dermatoses Basophilic leukocytes however, do not occur In myelosis (myeloid leukemia), in addition to polymorphonuclear leukocytes and eosinophilic leukocytes one finds immature myeloid cells—namely, myeloblasts and myelocytes

Myeloblast and Myelocyte The myeloblast is a large cell with nongranular cytoplasm and a round or oval, vesicular nucleus The myelocyte differs from the myeloblast mainly by having in its cytoplasm either neutrophilic or eosinophilic granules Myelocytes are always oxidase positive, while myeloblasts may be oxidase positive or oxidase negative (For a more detailed discussion, see page 191)

Polymorphonuclear Leukocyte The polymorphonuclear leukocyte, or neutrophil, has a lobated nucleus and contains fine neutrophilic granules in its cytoplasm This cell occasionally is referred to as a microphage because it is a small phagocytic cell with the ability to phagocytize bacteria only In contrast, the macrophage, a large phagocytic, histiocytic cell, also can take up particulate matter such as hemosiderin, melanin and lipid Because of their ability to phagocytize bacteria, numerous polymorphonuclear leukocytes are present in the skin in acute bacterial infections, e g, in erysipelas and folliculitis In addition, they are found in conspicuous numbers in acute dermatitis, allergic vasculitis (anaphylactoid purpura), erythema

' ' ' erythema nodosum and

' ' illed polymorphonuclear eosinophil is characterized by the presence of coarse round brilliant eosinophilic granules in its cytoplasm The granules are visible with routine stains but stand out more clearly when Giemsa's stain is used Its nucleus is lobated and thus has the same appearance as that of the polymorphonuclear leukocyte The cell is able to phagocytize bacteria Polymorphonuclear eosinophils form as such in the bone marrow

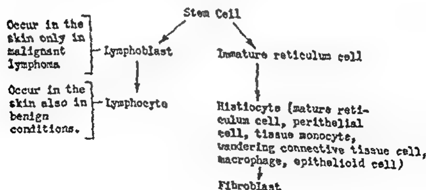
In addition to polymorphonuclear eosinophils monolobed eosinophils are observed not infrequently in pathologic conditions of the skin (Burkhart and Montgomery) Their nuclei are either oval kidney shaped or band shaped It is possible that they represent histiocytic eosinophils and as such are formed in the skin

Both the polymorphonuclear and the monolobed eosinophil occur in the tissue as a response to local anaphylaxis (Campbell) Tissue eosinophilia is apt to be prominent in eczematous drug eruptions atopic dermatitis dermatitis herpetiformis pemphigus vegetans allergic vasculitis (anaphylactoid purpura) eosinophilic granuloma granuloma faciale mycosis fungoides and Hodgkin's disease

LYMPHOID GROUP

It is widely accepted that lymphoid and reticular cells arise from a common cell—the lymphoid reticular stem cell (Chart 2)

CHART 2—Development of Lymphoid and Reticular Cells



Stem Cell The stem cell can be seen in the '

matin particles and one or two prominent nucleoli (see page 471 and Figure 260) This cell may develop into either a lymphoid cell (stem cell → lymphoblast → lymphocyte) or a reticular cell (stem cell → reticulum cell → histiocyte → fibroblast) (Gall and Mallory)

Lymphoblast. Lymphoblasts do not occur in ordinary inflammation of the skin but only in lymphoma They are spherical cells and possess a large nucleus surrounded by a uniform, basophilic rim of cytoplasm The nucleus is round or slightly indented (see page 477 and Figure 263) It is much larger and lighter than that of the mature lymphocyte

Lymphocyte. Lymphocytes have much smaller nuclei and less cytoplasm than lymphoblasts The nuclei are spherical and appear very darkly stained since the chromatin forms a thick layer at the periphery and several dark staining particles in the interior

Lymphocytes are found in the skin in most forms of lymphoma and in acute, subacute and chronic inflammations—for instance, in acute, subacute and chronic dermatitis, in psoriasis in lichen planus and in lupus erythematosus They also form a large proportion of the cells in most granulomas

It is probable that the lymphocytes present in the skin are hematogenous in origin, except in malignant *lymphoma, in which they may* arise autochthonously It is assumed by some authors that lymphocytes may *transform into histiocytes (Kolouch) Some believe even* that they may transform into fibroblasts (Goldsmith)

RETICULAR OR HISTIOCYTIC GROUP

The reticular or histiocytic group of cells belongs to the reticuloendothelial system The two outstanding properties of the reticular or histiocytic group of cells are their ability to absorb particulate matter and to produce reticulum fibers As the cells age they may change into fibroblasts (see Chart 2, page 33) As such, they no longer possess phagocytic powers and form collagen rather than reticulum

No generally accepted nomenclature exists for the reticular group of cells The following names are used by various authors as designation for the mature cell of this group histiocyte, reticulum cell, clasmatocyte, perithelial cell, tissue monocyte and wandering connective tissue cell The term histiocyte at present is employed the most widely Under special conditions, the histiocyte may become a macrophage or an epithelioid cell

Immature cells of the reticular groups are observed in *lymphoma* and generally are referred to as reticulum cells Therefore, lymphomas in which these cells predominate are called *reticulum cell*

lymphoma However, it should be kept in mind that many authors use the term reticulum cell also for mature reticular cells

Reticulum Cell (Immature Reticular Cell) This cell, as seen in reticulum-cell lymphoma possesses a nucleus which is smaller than that of a stem cell but larger than that of a histiocyte The nucleus may be round but usually is oval or kidney shaped It is pale staining and has a moderately heavy chromatin network and a distinct basophilic nuclear membrane (see page 174 and Figure 261) The cytoplasm is eosinophilic and abundant It often is irregular in outline and may show pseudopodic protrusions Because of their immaturity, the cells may form reticulum fibers only to a slight degree and have little or no phagocytic power

Histiocyte (Mature Reticular Cell) Histiocytes are formed in the skin in contrast to lymphocytes which do not arise in the skin except in malignant lymphoma

In the normal skin histiocytes are present in small numbers around the capillaries (perithelial cells) Under pathologic conditions which include the inflammatory diseases and the granulomas histiocytes tend to wander from the pericapillary regions into the dermis (tissue monocytes wandering connective tissue cells)

Histiocytes are much smaller than reticulum cells but otherwise do not differ from them in appearance Histiocytes form abundant reticulum fibers and possess the ability to phagocytize bacteria and particulate matter

Histiocytes may resemble fibroblasts greatly and often it is not possible to state with certainty whether a given cell is a histiocyte or a fibroblast As a rule however the nuclei of histiocytes are larger and stain slightly paler than those of fibroblasts Although both may have oval nuclei those of histiocytes tend to be kidney shaped those of fibroblasts spindle shaped While histiocytes possess the ability to form reticulum fibers fibroblasts form collagen It should be remembered that no sharp borderline exists between the histiocyte and the fibroblast since the histiocyte presents the *parent cell of the fibroblast* and may develop into a fibroblast

Macrophage Histiocytes possess the ability to phagocytize particulate matter and certain micro organisms Those containing phagocytized material are called macrophages Histiocytes migrate as wandering cells to areas where material digestible to them is present They may ingest melan[illegible]

or melanophor[illegible]

They may also [illegible]

bacteria fungi [illegible]

[illegible] Examples of bacteria which may be ingested by histiocytes are lepra bacilli and Frisch bacilli of

fungi, *Histoplasma capsulatum;* of viruses, Donovan bodies, and of protozoa, *Leishmania tropica* When individual macrophages are unable to deal with particles to be removed, they tend to fuse together and to form multinucleated foreign body giant cells Excellent examples of foreign body giant cells may be seen in paraffinoma gout and Malherbe's *calcifying epithelioma* The *nuclei in foreign* body giant cells usually are clumped together in an irregular arrangement, but they may lie regularly along the periphery of the cell, so that foreign body giant cells may be indistinguishable from Langhans giant cells

Epithelioid Cell. Under certain conditions, histiocytes may change into epithelioid cells Epithelioid cells possess a large, usually oval, pale, vesicular nucleus resembling the nucleus of epithelial cells and abundant, ill defined, slightly eosinophilic cytoplasm Pseudopodic elongations of the cytoplasm usually can be seen When lying in groups, the cytoplasm of neighboring cells often appears coalesced Epithelioid cells may form giant cells, the so called Langhans type of giant cell It is likely that this type of giant cell forms by amitotic *nuclear division without cellular division* The *nuclei are arranged* in an arc along the periphery of the cell in horseshoe fashion Epithelioid cells and Langhans giant cells have phagocytic power and have the ability to form reticulum fibers

Epithelioid cells are found in a variety of granulomas, especially in tuberculosis, sarcoidosis, leprosy, syphilis blastomycosis and coccidioidomycosis In tuberculosis epithelioid cells form as a tissue response to the lipid fraction of the tubercle bacillus (Sabin) As a granulomatous *lesion containing epithelioid cells heals, the epitheli* oid cells may mature into fibroblasts and their reticulum fibers into collagenous fibers This process can be observed particularly well in healing lesions of sarcoidosis

Fibroblast. The common (resting) connective tissue cells are called fibroblasts because they are instrumental in the elaboration of the collagenous fibers (see page 20) Their nuclei are elongated, often spindle shaped Because of their pale staining and the presence of a fine nuclear membrane, *the nuclei have a vesicular appearance* The cell body, which is spindle shaped is not discerned easily Fibroblasts usually are found adjacent to the surface of collagenous bundles

PLASMA CELLS

The plasma cell has abundant cytoplasm which is deeply basophilic, homogeneous and sharply defined The nucleus is eccentrically placed and round, and along its membrane shows coarse, dark stain

lished All stages of transition between reticulum cells and plasma cells can be observed in the spleen of rabbits after repeated intra venous injections of horse serum Antibodies are formed in great quantities in reticulum cells during their development into plasma cells while mature plasma cells have already passed the stage of greatest activity (Fagraeus) It is assumed by some that not only reticulum cells but also all multipotent cells of the connective tissue as well as lymphocytes are capable of transforming into a plasma cell (Campbell and Good)

Plasma cells occur in small numbers in most chronic inflammatory diseases of the skin and in larger number in granulomas They are particularly conspicuous in syphilis granuloma inguinale and rhino scleroma In the presence of many plasma cells but especially in rhinoscleroma round hyaline acidophilic bodies so-called Russell bodies may be found within and outside of plasma cells They form within plasma cells as a phenomenon of degeneration and finally are expelled (Pearse) They may attain a size twice that of a normal plasma cell (See also page 202)

MAST CELLS

Mast cells and basophilic leukocytes have nothing in common aside from an identical basophilic metachromatic staining reaction of their granules Th [illegible]
cyte a myeloid [illegible]
and have an ova [illegible]
and have a lobated nucleus

The granules of mast cells are soluble in ordinary fixatives such as Helly s and Zenker s fluids and do not stain with hematoxylin eosin Ten per cent Formalin absolute alcohol and saturated basic lead acetate are suitable as fixatives and methylene blue or Giemsa s stain is suitable for staining the granules The granules are basophilic (i e they stain with basic aniline dyes) and metachromatic (i e they may stain in a color different from that possessed by the dye) In this sense the bluish dye thionine stains the mast-cell granules a reddish violet toluidine blue stains them a purplish red and polychrome methylene blue stains them red (Michels)

Mast cells have two known functions secretion of hyaluronic acid and secretion of heparin That hyaluronic acid is present in the mast cell granules is proved by the observations that mast cell gran

ules stain exactly like hyaluronic acid and no longer show metachromatic staining after the tissue containing them has been submitted to the action of hyaluronidase (Asboe Hansen) Evidence for the presence of heparin in the mast cell granules is the similarity of reaction of the two substances to metachromatic staining and the parallelism existing between the amount of extractable heparin and the mast cell content of certain organs (Jorpes)

Mast cells occur everywhere in the connective tissue of the body particularly in the vicinity of capillaries and in the walls of larger blood vessels The normal skin contains relatively few mast cells which are small and spindle shaped As a rule they are arranged in groups around the blood vessels but they occur also around the hair follicles and in the papillary layer of the dermis Their number is *increased in many different conditions (Asboe Hansen) For instance* the granulation tissue in healing wounds contains more mast cells *than normally are present In most itching dermatoses such as atopic* eczema contact dermatitis and lichen planus an increased number of mast cells is present around the capillaries In lupus erythematosus in which there is an increase in the amount of hyaluronic acid in the dermis the number of mast cells closely parallels the intensity of metachromatic staining Also neurofibromas and the stroma of carcinomas of the skin contain numerous mast cells Thus an increase in mast cells is of no diagnostic significance except in urticaria pigmentosa where they occur in tumor like aggregates especially in the upper dermis

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6

Congenital Diseases (Genodermatoses)

ICHTHYOSIS

Two forms of ichthyosis occur *ichthyosis vulgaris* and *ichthyosis congenita* In ichthyosis vulgaris, the skin is dry and rough and shows



Fig 12 Ichthyosis vulgaris There are hyperkeratosis and absence of the granular layer The stratum malpighii is thin, the rete ridges irregular A large keratotic plug is located within a hair follicle (×100)

scaling, often in the form of large lamellae resembling fish scales Involvement is *severest on the extensor surfaces of the extremities,* while the flexures usually are spared Follicular hyperkeratoses are frequently present

Ichthyosis congenita is a more severe form of ichthyosis than

ichthyosis vulgaris The skin is represented by a thick horny cuirass with development of deep fissures

Ichthyosis hystrix is not related to ichthyosis but represents an extensive or systematized nevus verrucosus (see page 321)

Histopathology The characteristic lesion of ichthyosis vulgaris is hyperkeratosis with diminution or even complete absence of the granular layer (Fig 12) This represents an exception to the rule that an increase in thickness of the horny layer is accompanied by an increase in thickness also of the granular layer The probable reason for this exceptional finding is that in ichthyosis vulgaris there is an inadequate shedding rather than an overproduction of horny cells The hyperkeratosis in ichthyosis vulgaris is moderate and not associated with parakeratosis The stratum malpighii is thinner than normal and the rete ridges are diminished in number some are atrophic while others are slender elongated and branching (dove tailed) The hyperkeratosis usually affects also the upper portion of the hair follicles resulting in large follicular keratotic plugs. The pressure of the keratotic plugs causes atrophy of the lower portion of the follicles and of the sebaceous glands

Ichthyosis congenita differs from ichthyosis vulgaris only by showing a much greater degree of hyperkeratosis A stratum granulosum is usually present but it is not prominent

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

Like ichthyosis this disease is characterized by dryness roughness and scaling of the skin In addition generalized erythema is present and in many cases bullae occur In contrast to ichthyosis the flexural surfaces are involved most intensely

Histopathology In the erythematous areas of the skin one observes pronounced hyperkeratosis with occasional islands of parakeratosis A stratum granulosum is present Although it varies in thickness it is for the most part hypertrophic The stratum malpighii shows acanthosis with irregular elongation of the rete ridges The upper dermis shows a chronic inflammatory infiltrate

Examination of bullous lesions has revealed in some cases merely presence of a nonspecific subcorneal bulla (MacKee and Rosen) In others a pronounced ballooning of epidermal cells was noted either in the midportion of the epidermis (Ellis) or in the granular layer (Barker and Sachs) In the latter case the changes in the granular layer resembled those seen in epidermodysplasia verruciformis Ellis believes that the ballooning of epidermal cells is caused by a persistence of embryonal cells inasmuch as the cells of the embryonal stratum intermedium have a ballooned appearance (see page 4)

Differential Diagnosis. Congenital ichthyosiform erythroderma differs from ichthyosis by the presence of a usually *hypertrophic* granular layer, the presence of acanthosis and the presence of an inflammatory infiltrate in the dermis In ichthyosis, the granular layer is diminished in thickness or absent, the stratum *malpighii* is thinner than normal and no infiltrate is present in the dermis (Laymon and Murphy)

KERATOSIS PALMARIS ET PLANTARIS

This condition, which often is hereditary, is characterized by diffuse thickening of the horny layer of the palms and the soles Because of the formation of fissures, the condition causes great discomfort to the patient

Histopathology. The histologic picture is nonspecific, showing considerable hyperkeratosis as the only constant change Occasionally there also are acanthosis and a chronic inflammatory infiltrate in the upper dermis

KERATOSIS PUNCTATA PALMARIS ET PLANTARIS

Multiple, discrete, yellow to dark brown, firm, slightly elevated, conical keratotic plugs, 1 to 3 mm in diameter, are distributed symmetrically over the palms and the soles

Histopathology. One observes a circumscribed hypertrophy of the stratum corneum consisting of a cone shaped plug which invaginates the subjacent structures Beneath this plug the stratum malpighii is thinned The dermis is free of any inflammatory infiltrate (Scott, Costello and Simuango)

PACHYONYCHIA CONGENITA

This disease shows dystrophic changes of the nails, palmar and plantar hyperkeratosis, follicular keratosis and leukoplakia of the oral mucosa

A variety of pachyonychia congenita is *dyskeratosis congenita* It shares with pachyonychia congenita the dystrophic changes of the nails and the presence of leukoplakia However, there are no hyperkeratotic changes of the skin Instead the skin shows atrophy and patches of hyperpigmentation

Histopathology. In pachyonychia congenita one observes hyperkeratosis with areas of parakeratosis There is follicular plugging Occasionally, horn plugs are present also in the sweat ducts (Andrews) The granular layer is hypertrophic The stratum malpighii shows acanthosis with elongation of the rete ridges A mild chronic inflammatory infiltrate is present in the upper dermis Dyskeratotic

changes, similar to the corps ronds of Darier's disease, have been observed in the stratum malpighii of some cases (Andrews, Wright and Guequierre)

Dyskeratosis congenita shows thinning of the epidermis and almost complete absence of rete ridges In areas in which the skin shows hyperpigmentation, the amount of melanin in the basal layer is increased and melanophores are present in the upper dermis (Cole, Rauschkolb and Toomey)

POROKERATOSIS MIBELLI

One or several lesions may be present They show an atrophic center surrounded by a raised keratotic wall The wall has on its top a groove filled with keratotic material



Fig. 15 Porokeratosis Mibelli The section is taken from the keratotic wall It shows the *deep groove* which forms the center of the keratotic wall The groove is filled with a large *horn plug* (the "cornoid lamella") The cornoid lamella has a column of *parakeratotic cells* in its center On the right is a normal sweat duct

Histopathology. The atrophic center shows slight hyperkeratosis, atrophy of the stratum malpighii and fibrosis of the upper dermis The keratotic wall shows considerable hyperkeratosis and acanthosis In its center, the keratotic wall *presents* a deep groove filled by a large horn plug (the "cornoid lamella") This cornoid lamella has

in its center a column of parakeratotic cells Beneath the parakeratotic column the granular layer is absent elsewhere it is well developed The dermis underlying the cornoid lamella shows a chronic inflammatory infiltrate (Fig 13)

Owing to the presence of the cornoid lamella the histologic picture of porokeratosis is diagnostic The name porokeratosis is a misnomer since the cornoid lamella is not necessarily located in the opening of a sweat duct

XERODERMA PIGMENTOSUM

This disorder is associated with hypersensitivity to ultraviolet light The lesions occur chiefly on exposed areas of the skin An early and a late stage occur In the early stage one observes slight diffuse erythema with scaling and small areas of hyperpigmentation resembling freckles In the late stage atrophy of the skin mottled pigmentation and telangiectases are present giving the skin an appearance similar to that of chronic radiodermatitis Warty growths appear within the atrophic skin which may develop into carcinoma

Histopathology In the early stage the histologic appearance is not always characteristic the diagnosis often can be made from the combination of the histologic changes however There are (1) hyperkeratosis (2) thinning of the stratum malpighii with atrophy of some of the rete ridges and irregular proliferation and prolongation of others (3) edema of the upper dermis (4) a chronic inflammatory predominantly perivascular infiltrate in the upper dermis and (5) spotted melanin pigmentation of the basal layer with melanophores in the upper dermis

In the late stage the epidermis shows atrophy in some areas and acanthosis in others Atypical and multinucleated cells may be seen in the epidermis The hyperkeratosis and hyperpigmentation already present in the early stage are more pronounced The upper dermis shows degenerative changes of the collagen and of the elastic fibers of the same type as is seen in senile degeneration of the skin Thus one observes basophilic degeneration of the collagen and senile elastosis (see page 157) In some areas the epidermis may show atypical downward growth so that the histologic picture in such areas is identical with that of *senile keratosis*

Ultimately squamous-cell carcinomas and occasionally basal cell epitheliomas and sarcomas develop in some of the lesions

CONGENITAL ECTODERMAL DEFECT

This condition represents an incomplete development of the epidermis and its appendages The skin is smooth and glossy Hair

growth is sparse or completely absent. The facies is typical. It shows depressed nasal root and bridge, prominent frontal bosses and thick lips In addition, there may be dental aplasia and dystrophy of the nails Because of the diminution or the absence of sweat glands, the patient is unable to sweat adequately and therefore is intolerant to heat

Histopathology. There is either a total absence of sweat glands or the presence of rudiments of nonfunctioning glands and ducts There is usually a similar deficiency of pilosebaceous structures The epidermis is thinner than normal and there may be likewise a reduction in the width of the dermis The collagen, the elastic fibers and the blood vessels are normal in appearance, as a rule Examination of the axillary skin in two cases revealed total absence of eccrine glands, while the apocrine glands were developed normally (Sunderman)

ROTHMUND'S SYNDROME, WERNER'S SYNDROME (PROGERIA OF ADULTS) AND PROGERIA OF CHILDREN

These are three different, though related, genodermatoses in which

infancy with

the affected

skin shows erythema, scaling, telangiectases and brownish pigmentation so that the appearance of the skin resembles that of poikilo-

subcutaneous fat and the musculature of the *extremities* undergo atrophy leading on the legs to ulcerations Cataracts develop early in adult life

Progeria of children is not familial *It starts* several months after birth The patient develops into a dwarf with *a large skull* and bird like features The skin appears atrophic and *wrinkled*

Histopathology. No characteristic histologic features are seen in the skin in any of the three *diseases In all* of them, the skin merely shows atrophy of *the epidermis, thinning of the* collagen bundles in the dermis and atrophy or *even disappearance* of the cutaneous appendages (Reed) The areas of *erythema in* Rothmund's syndrome, in spite of their clinical *resemblance to* poikiloderma atrophicans vasculare, show no *inflammatory infiltrate but* merely atrophy and telangiectasis (Thannhauser)

in its center a column of parakeratotic cells Beneath the parakeratotic column the granular layer is absent elsewhere it is well developed The dermis underlying the cornoid lamella shows a chronic inflammatory infiltrate (Fig 13)

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scarring results In hydroa aestivale the changes in the dermis are less severe than in hydroa vacciniforme Therefore healing takes place without scar formation

EPIDERMOLYSIS BULLOSA

In this condition vesicles or bullae form usually at points of trauma but sometimes without trauma Three forms of the disease exist *epidermolysis bullosa simplex epidermolysis bullosa dystrophica* and *epidermolysis bullosa hereditaria letalis* The simple form is inherited dominantly and the other two forms recessively In the simple form the bullae heal without scarring the mucous membranes and the nails are rarely affected and the disease improves or even subsides at puberty In the dystrophic form the lesions heal with atrophic scars oral lesions and dystrophic changes of the nails are frequently present and the disease persists throughout life In the third form epidermolysis bullosa hereditaria letalis death usually occurs within the first 3 months of life The bullae show little tendency to heal but if they heal no scars remain Oral lesions and dystrophic changes of the nails are usually present

Histopathology The bullae are always in subepidermal location in the dystrophic form (Tulipan) and in the lethal form (Lamb and Halpert Schiffer) whereas in the simple form they may be found in subepidermal location (Leoni) in intra epidermal or in subcorneal location (Johnson and Test) However it is likely that also in epidermolysis bullosa simplex the bullae always form subepidermally but because of the tendency of the epidermis to rapid regeneration the cleavage will be found intra epidermally or subcorneally in bullae that are a few days old (This occurs not infrequently in erythema multiforme and in bullous pemphigoid see page 86) No significant inflammatory reaction is observed in the dermis unless secondary infection has occurred In the dystrophic form small milium like epidermal cysts may be found in the upper dermis (Tulipan)

Engman and Mook first described the absence of elastic fibers in the papillary and the subpapillary layers of involved as well as non involved areas They believed that the absence of elastic fibers was the cause of the disease Although some authors have confirmed this finding others have found the elastic tissue to be normal (Allen) In general it appears that in the simple form the elastic tissue is normal (Johnson and Test) while in the dystrophic form the elastic tissue tends to be absent in the upper dermis of the involved areas (Tulipan Lamb and Halpert) However it is probable that the absence of elastic tissue in the dystrophic form is not primary but secondary and is the result of its destruction by the disease process In

HYDROA VACCINIFORME AND HYDROA AESTIVALE

Hydroa is a recurring papulovesicular eruption occurring chiefly in the summer season, usually in boys, and solely on the exposed parts of the skin. Two forms exist: *hydroa aestivale*, the milder form, which does not produce scarring and ends at puberty, and *hydroa vacciniforme*, which produces scarring and persists as a rule through-

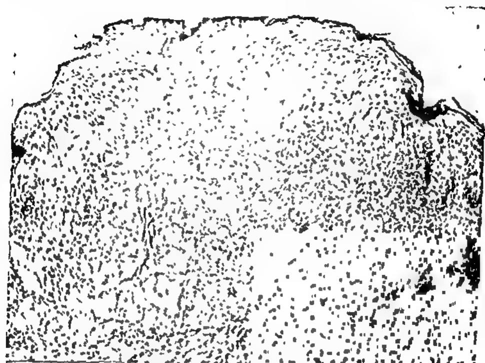


Fig. 14. Hydroa vacciniforme. There is a wedge-shaped area of necrosis involving the epidermis and the upper dermis It is walled off by a chronic inflammatory infiltrate. (×100)

out life. In about one third of the cases, hydroa vacciniforme is associated with congenital porphyria, i.e., excretion of large amounts of uroporphyrin and coproporphyrin in the urine (see page 278).

Histopathology. In hydroa vacciniforme, a focal area of inflammation followed by necrosis forms in the upper dermis (Fig. 14). In the overlying epidermis, an intra-epidermal vesicle develops which at first is multilocular, but later, because of the degeneration of epithelial cells, becomes unilocular. The vesicle is filled with fibrin, leukocytes and the débris of epithelial cells. Within the area of necrosis located in the upper dermis, the blood vessels are thrombosed and foci of hemorrhage occur. The necrotic area is walled off with a chronic inflammatory infiltrate. On absorption of the necrotic area,

and grains (2) formation of lacunae and (3) irregular upward proliferation of papillae into the lacunae resulting in the formation of villi (Fig 15) There also are papillomatosis, acanthosis and hyperkeratosis The dermis shows a chronic inflammatory infiltrate In



... the granular layer are several corps ronds (C.R.), characterized by large round homogeneous deep staining nuclei In the lower third within a lacuna are grains (G.) characterized by small often grain shaped nuclei (×400)

some cases in addition there is downward proliferation of epidermal cells into the dermis

The corps ronds occur mainly in the stratum malpighii and the granular layer while the grains occur mainly in the horny layer Both may be found within the lacunae Corps ronds possess large, round homogeneous deeply basophilic nuclei and a homogeneous (hyalinized) deeply eosinophilic cytoplasm lined by a distinct membrane They are much larger than normal squamous cells (Fig 16) Corps

any case, recent studies of normal elastic tissue indicate that it plays no part in the coherence between epidermis and dermis (see page 8).

Differential Diagnosis. Differentiation of epidermolysis bullosa from other bullous diseases often is impossible The presence of small epidermal cysts and the absence of elastic tissue, however, may aid in the establishment of the diagnosis

DARIER'S DISEASE (KERATOSIS FOLLICULARIS)

This disease is characterized by a more or less extensive eruption consisting of hyperkeratotic or crusted papules which by confluence



Fig 15 Darier's disease Low magnification There are hyperkeratosis and papillomatosis Numerous lacunae (L) are present On the left are elongated papillae lined by only one layer of cells so called villi (V) Corps ronds (C R) are present in the granular layer and grains (G) in the horny layer and in some of the lacunae *(×100)*

may form verrucous, crusted areas Occasionally, hypertrophic lesions are present with elevated, verrucous formations The oral mucosa is commonly, and the vulva, the larynx and the pharynx occasionally, involved (Brunauer)

Histopathology. The characteristic changes in Darier's disease are (1) a peculiar form of dyskeratosis, namely, formation of corps ronds

tion, two rows of epithelial cells line the villi. Furthermore, no dyskeratosis occurs and large apocrine glands are present in the dermis

FAMILIAL BENIGN CHRONIC PEMPHIGUS
(Hailey and Hailey)

This disease (which often, but not always, is familial) is characterized by a localized recurrent eruption of vesicles and bullae By peripheral extension, the lesions may assume a circinate configuration

Histopathology. Although early lesions may show like Darier's disease small suprabasal separations so-called lacunae fully devel



Fig 17 Familial benign chronic pemphigus (Hailey and Hailey) The bulla is suprabasal in position One observes loss of intercellular bridges resulting in considerable acantholysis and formation of villi (upward growth of papillae) These features cause a surprising resemblance to the bulla of pemphigus vulgaris (×200)

oped lesions show large separations, namely bullae in suprabasal position (Fig 17) Villi i e, elongated papillae lined by a single layer of basal cells protrude upward into the bullae and, in some cases, cords of basal cells proliferate downward into the dermis The bullae con

ronds develop on account of premature partial keratinization of the cell prior to reaching the horny layer, a process called benign dyskeratosis. (Malignant dyskeratosis is observed in Bowen's disease and in squamous cell carcinoma.)

The grains are small cells, considerably smaller than the corps ronds. They resemble parakeratotic cells except that their nuclei are more prominent. The nuclei are elongated, often grain shaped.

The lacunae represent small, slitlike, intra-epidermal vesicles which are found most commonly directly above the basal layer. They contain desquamated, acantholytic epidermal cells which have lost their intercellular bridges due either to degenerative changes or to partial keratinization. Corps ronds and, especially, *grains are present among* these desquamated cells.

Elongated, often tortuous papillae lined usually with but a single layer of basal cells project into the lacunae. They often are referred to as villi.

The hyperkeratosis and the papillomatosis cause the formation of keratotic plugs. They often fill the pilosebaceous follicles but also are found outside of follicles. Darier's disease, therefore, is not, as Darier originally thought, primarily a follicular disease. Proof of this is the fact that areas devoid of follicles, such as palms, soles and oral mucosa, may be affected (Ellis). The term keratosis follicularis is, then, a misnomer.

In some cases of Darier's disease, but especially in those with hypertrophic lesions, one observes considerable downward proliferation of the epidermis, either as a proliferation of basal cells or as pseudoepitheliomatous hyperplasia (Beerman). The proliferations of basal cells consist of long narrow cords composed of two rows of basal *cells between which there may or may not* be a lacunar space. These proliferations may send out branches and may penetrate deep into the dermis. *The pseudoepitheliomatous hyperplasia may suggest* squamous cell carcinoma, but, so far, no case of Darier's disease resulting in malignancy *has been reported. (For a discussion of pseudo-*epitheliomatous hyperplasia see page 334.)

The lesions on the oral and other mucous membranes are analogous to those observed on the skin except that hyperkeratotic changes are mild or absent (Brunauer).

Differential Diagnosis. For the differentiation of Darier's disease from familial benign chronic pemphigus see below. The villous proliferations into the lacunar spaces may resemble those of syringocystadenoma papilliferum (Beerman). However, in the latter condi-

casionally into basal cell epithelioma (Sullivan and Ellis) or squamous-cell carcinoma (Costa and Junqueira; Ormea).

In 1946, Lutz (one of the original describers), on the basis of successful implantation tests, stated that epidermodysplasia is "not an independent dermatosis, but rather a generalized eruption of warts with somewhat peculiar characteristics" Yet, some authors, though conceding that Lutz' case was one of verrucae planae, still regard epidermodysplasia verruciformis as an entity (Ormea; Teodorescu, Midana) Midana obtained negative results in auto inoculation experiments performed on two patients Teodorescu found in two patients associated with the epidermodysplasia verruciformis, keratosis palmaris et plantaris hereditaria and regarded both diseases as genodermatoses

ACROKERATOSIS VERRUCIFORMIS

(Hopf)

Numerous hyperkeratotic and occasionally verrucous papules are present, predominantly on the dorsa of the hands and the feet

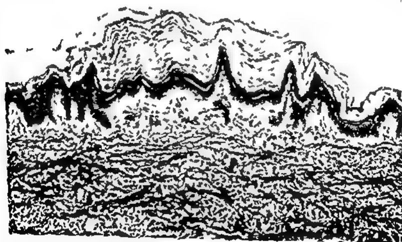


Fig 18 Acrokeratosis verruciformis (Hopf) The lesion consists of a circumscribed area of papillomatosis, acanthosis and hyperkeratosis (×100)

Histopathology. The papules show considerable hyperkeratosis, increase in thickness of the granular layer and acanthosis (Fig 18) In addition, there are slight papillomatosis and some thickening of the rete ridges The rete ridges all extend to a uniform level and their configuration is well preserved There is no parakeratosis or

thin acantholytic cells some of which show evidence of keratinization Occasionally there is evidence of dyskeratosis namely shrinking of some of the acantholytic cells which then assume the appearance of grains However corps ronds have been described in only a few cases (Ellis Winer and Leeb)

Differential Diagnosis Familial benign chronic pemphigus shares certain histologic features with both *Darier s disease and pemphigus vulgaris* In all three diseases one finds suprabasal separations of the epidermis caused by acantholysis and upward proliferation of papillae as so called villi into the resulting lacunae or bullae Familial benign chronic pemphigus however differs from Darier s disease by the larger size of the suprabasal *separations (which thus appear as bullae* rather than as lacunae) and the lesser degree or even the absence of dyskeratosis If dyskeratosis is absent differentiation from pemphigus vulgaris may be impossible Occasionally however one observes in familial benign chronic pemphigus even in the absence of *dyskeratosis an early onset of keratinization in the lower layers of* the detached epidermis The presence of eosinophils in the bullae points toward a diagnosis of pemphigus vulgaris but their absence does not rule it out

The nosologic position of the disease is at present uncertain The *presence of dyskeratotic changes in most cases of familial benign* chronic pemphigus has led some observers to regard this disease as a bullous variant of Darier s disease (Ellis Tannerud and Szymanski Winer and Leeb) However until more is known about the cause of the disease it may be best to regard it as an independent entity *(Hailey and Hailey Frank and Rein)*

EPIDERMODYSPLASIA VERRUCIFORMIS

(Lewandowsky and Lutz)

In this dermatosis one finds an extensive eruption of flat topped hyperkeratotic lesions resembling verrucae planae *By confluence* lichenified plaques may form

Histopathology The histologic changes consist of hyperkeratosis increase in the thickness of the granular layer acanthosis and a peculiar vacuolization of the cells in the upper layers of the stratum malpighii of the granular *cells and of the horny cells Because of* the vacuolization the horny layer shows a loosely felted basket weave pattern *The histologic* picture is like that of verruca plana (Fig 122) with two exceptions (1) in epidermodysplasia verruciformis the nuclei of the vacuolated cells show more pronounced pyknosis and *fragmentation* than in verruca plana (Sullivan and Ellis Waisman and Montgomery) and (2) the lesions change oc

casionally into basal cell epithelioma (Sullivan and Ellis) or squamous cell carcinoma (Costa and Junqueira, Ormea)

In 1946, Lutz (one of the original describers), on the basis of successful implantation tests, stated that epidermodysplasia is "not an independent dermatosis, but rather a generalized eruption of warts with somewhat peculiar characteristics" Yet, some authors, though conceding that Lutz' case was one of verrucae planae, still regard epidermodysplasia verruciformis as an entity (Ormea, Teodorescu, Midana) Midana obtained negative results in auto inoculation experiments performed on two patients Teodorescu found in two patients, associated with the epidermodysplasia verruciformis, keratosis palmaris et plantaris hereditaria and regarded both diseases as genodermatoses

ACROKERATOSIS VERRUCIFORMIS

(Hopf)

Numerous hyperkeratotic and occasionally verrucous papules are present, predominantly on the dorsa of the hands and the feet

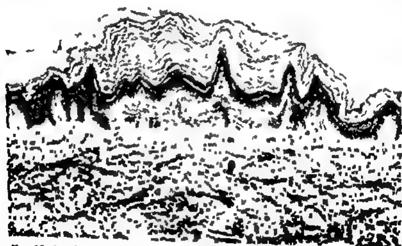


Fig 18 Acrokeratosis verruciformis (Hopf) The lesion consists of a circumscribed area of papillomatosis, acanthosis and hyperkeratosis (X100)

Histopathology. The papules show considerable hyperkeratosis, *increase in thickness of the granular layer* and acanthosis (Fig 18) In addition, there are *slight papillomatosis* and some thickening of the rete ridges *The rete ridges all extend to a uniform level and their configuration is well preserved* There is no parakeratosis or

vacuolization of cells such as is seen in verruca vulgaris and verruca plana (Loveman; Niedelman).

PSEUDOXANTHOMA ELASTICUM

This disorder represents a congenital defect of the elastic tissue which may be limited in extent or widespread In addition to the elastic tissue in the dermis, the elastic membrane of the retina, called

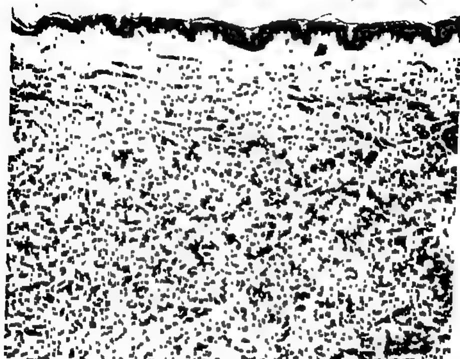


FIG 19 **Pseudoxanthoma elasticum.** Low magnification, Verhoeff stain This illustration shows the usually observed late degenerative stage In the lower dermis, the elastic fibers are increased in number, appear swollen and show signs of degeneration, such as fragmentation, disintegration and clumping (Patient's age, 31 years) (×50)

Bruch's membrane, and the elastic fibers in the aorta, the arteries and the arterioles may be affected The degeneration of the elastic fibers of Bruch's membrane causes small defects and breaks which manifest themselves clinically as angioid streaks (Urbach and Wolfram, Hagedoorn, Ebert) Involvement of the aorta causes diffuse dilatation (Urbach).

The cutaneous lesions consist of soft, yellowish papules and plaques The papules frequently show a linear arrangement The sides of the neck are the most common site of the lesions

Histopathology. *Histologic examination of the skin reveals the elastic tissue to be normal in the subepidermal portion of the dermis*

In the middle and lower portions of the dermis, however, it is in creased, usually in circumscribed areas Within these areas, the elastic fibers are swollen and show
tion, disintegration and clu
eration and imbibition with
a basophilic staining and become visible with routine stains Fin

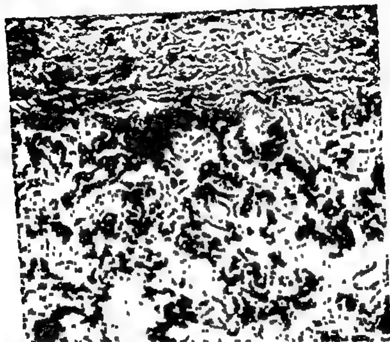


Fig 20 Pseudoxanthoma elasticum High magnification of *Figure 19* Verhoeff stain The elastic fibers are degenerated whereas the collagen shows no evidence of *degeneration (×200)*

nerud and Nomland have shown by staining methods (von Kossa's stain for calcium) and Lobitz and Osterberg by micro incineration that the degenerated elastic fibers are richly infiltrated with calcium The collagen fibers are unaltered

In a few instances the elastic tissue of the arterioles and the small arteries in the deep dermis was found to have undergone a similar degeneration (Urbach, de Sá Penella and Esteves)

It appears that pseudoxanthoma elasticum occasionally is preceded by an early hyperplastic stage (Fig 21) In this stage, which seems *to* be present only *during infancy* and childhood, the elastic fibers are increased in number and size but show no evidence of degeneration

as they do in the more commonly observed late degenerative stage (Weidman, Anderson and Ayres, Pautrier)

Differential Diagnosis. Senile elastosis, like pseudoxanthoma elasticum, shows a great increase in material taking the elastic tissue stain However, in senile elastosis this material is located in the upper third



Fig 21 Pseudoxanthoma elasticum Low magnification, Verhoeff stain This illustration shows the early hyperplastic stage The elastic fibers are large and swollen but show no evidence of degeneration (Patient's age, 2 years) (×100)

of the dermis and is present as dense masses rather than as individual curls Furthermore, staining of this material for calcium is always negative in senile elastosis

CUTIS HYPERELASTICA (EHLERS DANLOS SYNDROME)

This syndrome consists of (1) hyperelasticity of the skin, (2) hyper extensibility of the joints, (3) fragility of the skin and the blood vessels with formation of atrophic scars and (4) development of raisin like pseudotumors The pseudotumors form at points of trauma and are soft and pigmented and present a wrinkled surface

In many cases small, hard, subcutaneous nodules have been described They also are the result of trauma.

The collagen bundles appear atrophic, split up and separated by edema The elastic fibers are normal in some cases but in most cases show breaking up and clumping The amount of elastic tissue often appears increased but it is likely that this increase is not a real one but is simulated by the atrophy of the collagen In addition, the number of capillaries is increased and their lumina dilated Large, round cystic spaces representing lymphangiectatic cavities may occur (Korting and Gottron)

The raisinlike pseudotumors that are part of the syndrome form at areas of traumatic hemorrhage and consist either of accumulations of foreign body giant cells (Ronchese) or of proliferated connective tissue with large numbers of vessels in it The hard subcutaneous nodules contain calcified necrotic fat or mucoid material enclosed in a thick fibrous capsule (Johnson and Falls)

URTICARIA PIGMENTOSA

This disorder is characterized in most cases by the presence of a great number of brown macules scattered over the entire cutaneous surface When rubbed with a blunt instrument, they become distinctly urticarial In rare instances the lesions consist of one or several soft nodules or plaques

Histopathology The histologic picture shows an infiltrate composed chiefly of mast cells Mast cells are characterized by *the presence* of basophilic metachromatic granules in their cytoplasm (see pages 37 38) These granules are not visible on staining with *routine* stains Their demonstration requires special staining *(see pages 28 29* and Plate I) Fixation in 10 per cent Formalin (*without* subsequent exposure to Helly s solution) and staining with Giemsa s *stain* or with methylene blue are recommended

In the macular type mast cells are present in the upper *third* of the dermis especially around *the capillaries* Some appear to be round or oval but the majority are spindle-shaped Since in sections stained with hematoxylin and eosin the mast cells resemble fibroblasts the diagnosis may be missed easily *unless special* staining is employed

In the nodular type (Figs. 22 23) mast cells lie closely packed in tumorlike aggregates The infiltrate may extend *through* the entire dermis into the subcutis Wherever the mast *cells lie* in dense aggregates they are cuboidal rather than spindle shaped and show ample, slightly eosinophilic cytoplasm Because of their shape and ample

cytoplasm, they look unlike any other cell and the *diagnosis can be* made without resorting to special staining

If a biopsy is performed shortly *after the lesion has been stroked,* the section will show edema, an influx of eosinophils and shrinking of the mast cells associated with a great decrease in the amount of

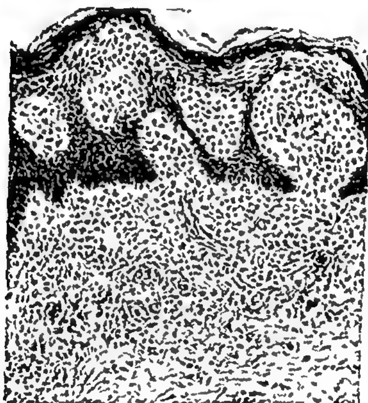


Fig 22 I [illegible] Low magnification [illegible] losely packed in [illegible] hape *Because of staining with hematoxylin eosin* the granules in the mast cells are not visible (×200)

granules within them indicating that the granules have been expelled from the cells (Drennan) There may even be disintegration and a temporary disappearance of mast cells which may be the explanation for certain reports in the literature where in otherwise typical cases of urticaria pigmentosa mast cells have not been found (Drennan and Beare)

The pigmentation of urticaria pigmentosa is due not to the presence of the mast cells but to melanin which is present in increased amounts in the basal layer and occasionally also in melanophores

The presence of extracutaneous lesions in urticaria pigmentosa has been reported recently However, the systemic lesions in Ellis'

case may well have been lymphoma, and the bone lesions in Sagher's and Clyman's cases were not examined histologically



FIG 23 Urticaria pigmentosa, nodular type High magnification of Figure 22 hematoxylin eosin stain The mast cells appear as large cuboidal cells (×400)

INCONTINENTIA PIGMENTI

The disease frequently begins immediately after birth *with inflammatory* lesions, particularly bullae, in linear and grouped arrangement The bullae may recur for months *They finally give* way to areas of pigmentation There may be an *intermediary stage* of linear verrucous lesions The pigmented areas are widely disseminated, located especially on the trunk, and have an irregular, bizarre outline

Histopathology. In the early vesicular stage, *one observes* intraepidermally located vesicles *containing many* eosinophils (Carney, Epstein, Vedder and Pinkus) In *addition, there* is spongiosis of the epidermis, and in the dermis an infiltrate composed of [illegible]

[illegible]

sp [illegible]

The final stage shows diminution or absence of melanin in the basal layer of the epidermis and extensive *deposits of* melanin inside

cytoplasm, they look unlike any other cell and the diagnosis can be made without resorting to special staining

If a biopsy is performed shortly after the lesion has been stroked, the section will show edema, an influx of eosinophils and shrinking of the mast cells associated with a great decrease in the amount of

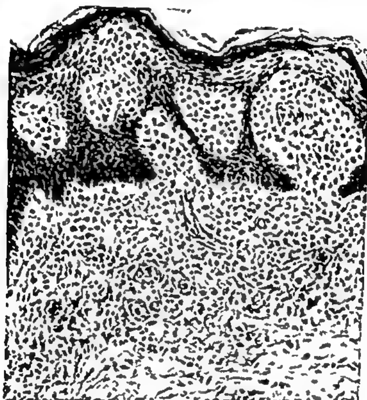


FIG 22 Urticaria pigmentosa, nodular type Low magnification hematoxylin eosin stain Mast cells lie closely packed in the upper dermis They are cuboidal in shape Because of staining with hematoxylin eosin the granules *in the mast cells are not visible (×200)*

granules within them indicating that the granules have been expelled from the cells (Drennan) There may even be disintegration and a temporary disappearance of mast cells which may be the explanation for certain reports in the literature where in otherwise typical cases of urticaria pigmentosa mast cells have not been found (Drennan and Beare)

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and outside of melanophores in the upper dermis In many cases the basal cells show degeneration and vacuolization It is believed generally that the disease causes damage to the cells in the basal layer so that the melanocytes become incapable of holding and metabolizing melanin (Sulzberger, Doornink)

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(See also Chapter 5 Mast Cells page 38)

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TABLE 2.—CLASSIFICATION OF VESICLES AND BULLAE

TYPE OF VESICLE OR BULLA	MODE OF FORMATION	SITE OF FORMATION	DISEASES
Subcorneal bulla	Detachment of horny layer	Subcorneal	Impetigo
Spongiotic bulla	Cellular necrosis followed by spongiosis and, occasionally, by reticular degeneration	Intra epidermal	Dermatitis-Eczema Pompholyx Congenital ichthyosiform erythroderma Hydroa
Miliarial bulla	Retention of sweat	Intracorneal Intra-epidermal or subepidermal	Miliaria crystallina Miliaria rubra
Acantholytic bulla	Acantholysis	Intra epidermal a suprabasal	Pemphigus vulgaris Pemphigus vegetans Familial benign chronic pemphigus Darier's disease Senile keratosis
		b upper epidermis	Pemphigus foliaceus Pemphigus erythematosus
5 Viral bulla	Reticular and ballooning degeneration with acantholysis	Intra-epidermal	Variola Herpes simplex Herpes zoster Varicella
6 Pressure bulla	Detachment of entire epidermis	Subepidermal	Bullous pemphigoid Benign mucous membrane pemphigoid Dermatitis herpetiformis Erythema multiforme Epidermolysis bullosa Porphyria cutanea tarda
7 Bulla due to basal cell degeneration	Degeneration of basal cells	Subepidermal	Incontinentia pigmenti Lichen planus Lichen sclerosus et atrophicus Lupus erythematosus
8 Bulla due to reticulum degeneration	Degeneration of subepidermal reticulum fibers	Subepidermal	Burns

7

Noninfectious Vesicular and Bullous Diseases

Several new concepts have been introduced in recent years concerning the histologic structure of vesicles and bullae and their mechanism of formation It appears appropriate therefore to present a classification of the different types of vesicles and bullae and to outline briefly their mode of formation before discussing individual diseases (Since from a histologic point of view it is immaterial whether a lesion is a vesicle or a bulla only the latter term will be used in the following presentation)

Eight distinct types of bullae can be recognized (Table 2)

1 *Subcorneal bulla* Detachment of the horny layer from the stratum malpighii occurs

2 *Spongiotic bulla* Liquefaction necrosis of a few epidermal cells causes formation of a minute cavity (vesiculette primordiale) which subsequently due to intercellular edema (spongiosis) and intracellular edema (alteration cavitaire) in the surrounding epidermis enlarges into an intra epidermal bulla In the case of pronounced intracellular edema reticular degeneration of the epidermis may occur (For a detailed description see page 69)

3 *Miliarial bulla* In miliaria bullae form due to the escape of sweat from the sweat ducts Two types occur miliaria crystallina in which the bulla is located within the stratum corneum and miliaria rubra in which the bulla forms either within the stratum malpighii or beneath the epidermis In severe cases of miliaria rubra the sweat duct ruptures (For a detailed description see page 76)

4 *Acantholytic bulla* Degeneration of intercellular bridges causes loss of coherence between epidermal cells and formation of rifts which enlarge into bullae Detached (acantholytic) epidermal cells are present in the bulla cavity Acantholysis may take place within the lower epidermis predominantly right above the basal layer or within the upper epidermis predominantly within the granular layer (For a detailed description see pages

TABLE 2.—Classification of Vesicles and Bullae

Type of Vesicle or Bulla	Mode of Formation	Site of Formation	Diseases
Subcorneal bulla	Detachment of horny layer	Subcorneal	Impetigo
Spongiotic bulla	Cellular necrosis followed by spongiosis and, occasionally, by reticular degeneration	Intra-epidermal	Dermatitis-Eczema Pompholyx Congenital ichthyosiform erythroderma Hydroa
Miliarial bulla	Retention of sweat	Intracorneal Intra-epidermal or subepidermal	Miliaria crystallina Miliaria rubra
Acantholytic bulla	Acantholysis	Intra-epidermal a. suprabasal	Pemphigus vulgaris Pemphigus vegetans Familial benign chronic pemphigus Darier's disease Senile keratosis
		b. upper epidermis	Pemphigus foliaceus Pemphigus erythematosus
5. Viral bulla	Reticular and ballooning degeneration with acantholysis	Intra-epidermal	Variola Herpes simplex Herpes zoster Varicella
6. Pressure bulla	Detachment of entire epidermis	Subepidermal	Bullous pemphigoid Benign mucous-membrane pemphigoid Dermatitis herpetiformis Erythema multiforme Epidermolysis bullosa Porphyria cutanea tarda
7. Bulla due to basal cell degeneration	Degeneration of basal cells	Subepidermal	Incontinentia pigmenti Lichen planus Lichen sclerosus et atrophicus Lupus erythematosus
8. Bulla due to reticulum degeneration	Degeneration of subepidermal reticulum fibers	Subepidermal	Burns

5 *Viral bulla* Invasion of epidermal cells by certain viruses causes two types of degenerative changes in epidermal cells ballooning and reticular degeneration Ballooning degeneration leads to extensive acantholysis Although the bullae form within the epidermis progression of the ballooning degeneration leads to a subepidermal location in older bullae (For a detailed description see page 239)

6 *Pressure bulla* Detachment of the entire epidermis from the dermis occurs Pressure of the accumulating tissue fluid often causes in early bullae *rounding of the lateral walls and stretching of the* epidermal cells located there Older bullae due to regeneration of the epidermis at the floor of the bulla may have an intra epidermal location If in addition disintegration of the detached stratum malpighii occurs the bulla may be subcorneal in location (For a detailed description see page 86)

7 *Bulla due to basal cell degeneration* Several diseases (see Table 2) cause hydropic degeneration of the basal cells This may result in damage to the cytoplasmic processes which effect the coherence of the basal cell layer with the dermis Thus a subepidermal bulla may form (For a detailed description see page 296)

8 *Bulla due to reticulum degeneration* Damage to the subepidermal feltwork of reticulum fibers causes the cytoplasmic processes of basal cells to pull out of this feltwork A subepidermal bulla forms into which numerous cytoplasmic processes extend from the basal cells at the roof of the bulla (For a detailed description see page 90)

DERMATITIS ECZEMA

The terms dermatitis and eczema now are used generally as synonyms They refer to an inflammation of the skin based on an allergic response of the skin to a variety of agents such as chemicals proteins bacteria and fungi The exciting allergen may act on the skin either from the outside or from the inside

Dermatitis or eczema may be acute subacute or chronic The clinical picture is characterized by polymorphism of the eruption Among the primary lesions that may be observed are macules papules and vesicles the macules and papules tend to coalesce to form areas of diffuse erythema Among the secondary lesions are scaling crusting lichenification and fissuring The lesions of dermatitis usually are not demarcated sharply but merge gradually into the surrounding normal skin Moderately severe to severe itching is present in most forms of dermatitis

No generally accepted classification of dermatitis exists and many cases defy assignment to any definite type In this section the following types of dermatitis will be discussed (1) contact dermatitis

(2) nummular eczema (3) atopic dermatitis (or neurodermatitis disseminata) (4) lichen simplex chronicus (or neurodermatitis circumscripta) (5) exudative discoid and lichenoid chronic dermatosis (6) seborrheic dermatitis including Leiner s disease (7) stasis dermatitis and (8) generalized exfoliative dermatitis In addition lesions of dermatitis may occur in superficial fungus infections as drug eruptions and in lymphoma The latter three forms of dermatitis will be discussed when the respective diseases are described

Contact dermatitis is caused by contact of the skin with an agent that acts either as a specific allergic sensitizer or as a primary irritant Contact dermatitis may be acute, subacute or chronic In acute and subacute contact dermatitis diffuse erythema edema oozing and crusting predominate in addition vesicles are often present if a specific allergic sensitizer is the cause In chronic contact dermatitis erythema scaling and lichenification prevail

Nummular eczema probably caused by a temporary loss of resistance in the skin to the ordinary bacterial flora of the skin presents fairly sharply demarcated patches of erythema studded with discrete pinpoint vesicles or pinpoint erosions

Atopic dermatitis a constitutional familial dermatosis of unknown cause which often is aggravated by emotional tension or allergic factors shows lichenified and scaling erythematous areas which when active show also oozing and crusting but no vesicles

Lichen simplex chronicus shows one or several lichenified plaques with little scaling Oozing and vesiculation are absent On the lower legs especially lichen simplex chronicus may become hypertrophic and assume a verrucous nodular appearance (lichenificatio gigantea lichen corneus hypertrophicus)

Exudative discoid and lichenoid chronic dermatosis shows ...
lesions wi...
and later
sent an er... of nummular eczema

Seborrheic dermatitis shows fairly sharply demarcated brownish red areas which show only little infiltration and are covered with fine greasy scales Oozing may be present but no vesiculation is found Generalized seborrheic dermatitis in infants often is referred to as Leiner s disease

Stasis dermatitis presents erythema edema scaling and occasionally oozing and crusting It differs from other forms of dermatitis first by showing brownish pigmentation due to hemosiderin depos...
second by res...

ski...
... scaling and in severe cases

oozing. It represents a peak reaction to which several forms of dermatitis may lead—for instance, contact dermatitis, atopic dermatitis, seborrheic dermatitis, stasis dermatitis, drug dermatitis and lymphoma dermatitis However, it may occur as an idiopathic disease

Histopathology. The various types of dermatitis rarely present a histologic picture sufficiently diagnostic to allow their differentiation



Fig 21 Acute dermatitis contact dermatitis due to poison ivy. Numerous intraepidermally located vesicles and marked intracellular edema are present The vesicles are separated by thin septa formed by *the resisting walls of edematous epidermal cells (reticular degeneration)* and thus form a multilocular bulla (×100)

because the same histologic reactions occur in all forms of dermatitis exudation leading to vesiculation in the acute stage, proliferation leading to acanthosis in the chronic stage, and a combination of these two reactions in the subacute stage Since, as a rule, no more specific diagnosis than acute, subacute or chronic dermatitis can be made, the histologic picture as presented by an acute, subacute and chronic dermatitis will be described first Thereafter, the distinctive features occasionally presented by the various members of the dermatitis eczema group will be discussed

In acute dermatitis, intra epidermally located vesicles or bullae predominate the histologic picture Considerable intercellular edema (spongiosis) and intracellular edema (altération cavitaire) may be present in the epidermis surrounding the vesicles If the number of

vesicles is great and the intracellular edema pronounced the vesicles due to reticular degeneration of the epidermis will be separated from one another only by thin septa formed by the resisting walls of edematous epidermal cells and will thus form a multilocular bulla (Fig 24) The vesicles and the bullae contain a few lymphocytes eosinophils and neutrophils and disintegrated epidermal cells Migrating lymphocytes and neutrophils are present in the epidermis The cells of the stratum corneum may be parakeratotic and intermingled with fibrin and numerous neutrophils (Winer and Lip-

vascular dilatation edema and a

neutrop

formation of the vesicles and the

had been

the vesicles

necrosis is

the primary factor and that spongio In 1925 Civatte described as the primary lesion the vesiculette primordiale formed by the lysis of two or three squamous cells through cytoplasmic alteration Spongiosis followed this and caused enlargement

expressed the same

upport vesicles tend

to form in areas where the rete cells liquefied vesicles often lie in areas formerly occupied by epidermal cells (Fig 25) and spongiosis may be entirely absent in the vicinity of vesicles Polak and Mom studying the formation of vesicles in experimental eczema with the aid of silver impregnation found that at the time the vesiculette primordiale formed the intercellular bridges were still intact and only broke later by mechanical force when the vesicle had increased in size

Differentiation of acute vesicular or bullous dermatitis from bullous erythema multiforme and dermatitis herpetiformis is not always possible Although in the latter two diseases the bullae form subepidermally they may be located intra epidermally during the stage of healing due to regeneration of the epidermis In that case secondary findings such as the presence of marked spongiosis in contact dermatitis and its absence in the other two diseases and the number of eosinophils may aid in the decision It should be stressed as of utmost importance that for the diagnosis of all vesicular and bullous diseases an early lesion must be chosen for histologic examination because secondary factors such as regeneration and pyogenic infection may obscure the diagnostic features

oozing. It represents a peak reaction to which several forms of dermatitis may lead—for instance, contact dermatitis, atopic dermatitis, seborrheic dermatitis, stasis dermatitis, drug dermatitis and lymphoma dermatitis. However, it may occur as an idiopathic disease.

Histopathology. The various types of dermatitis rarely present a histologic picture sufficiently diagnostic to allow their differentiation

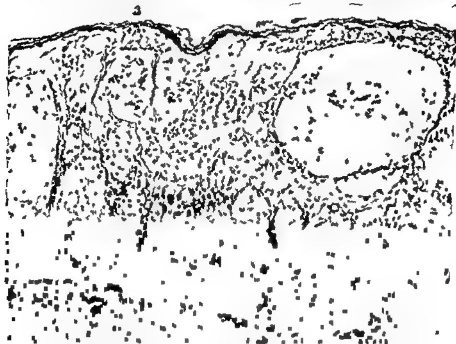


Fig. 24. Acute dermatitis, contact dermatitis due to poison ivy. Numerous intraepidermally located vesicles and marked intracellular edema are present. The vesicles are separated by thin septa formed by the resisting walls of edematous epidermal cells (reticular degeneration) and thus form a multilocular bulla. (×100)

because the same histologic reactions occur in all forms of dermatitis: exudation leading to vesiculation in the acute stage, proliferation leading to acanthosis in the chronic stage, and a combination of these two reactions in the subacute stage. Since, as a rule, no more specific diagnosis than acute, subacute or chronic dermatitis can be made, the histologic picture as presented by an acute, subacute and chronic dermatitis will be described first. Thereafter the distinctive features occasionally presented by the various members of the dermatitis eczema group will be discussed.

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Sachs Miller and Gray (1946) to the histologic picture as described above for chronic dermatitis because it is characteristically present in neurodermatitis disseminata (atopic dermatitis) and neurodermatitis circumscripta (lichen simplex chronicus) However the same histologic picture may occur in any dermatosis belonging to the dermatitis eczema group

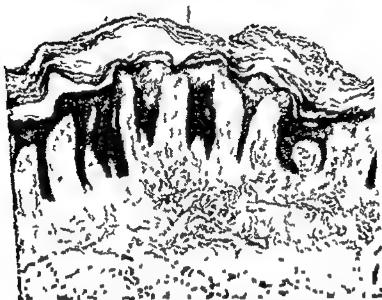


Fig 76 Chronic dermatitis neurodermatitis circumscripta There are hyperkeratosis acanthosis, elongation of the rete ridges and elongation and broadening of the papillae The dermis shows a chronic inflammatory infiltrate and fibrosis (×50)

Many diseases not members of the dermatitis eczema group show either regularly or occasionally a histologic picture allowing no more specific diagnosis than chronic dermatitis Diseases which regularly show the nonspecific histologic picture of chronic dermatitis include pityriasis rosea parapsoriasis and pellagra Many other diseases such as psoriasis, lichen planus and lupus erythematosus to name but a few show a diagnostic histologic picture in clinically typical cases but may show a nonspecific histologic picture that of chronic dermatitis in clinically atypical cases

Early mycosis fungoides must always be kept in mind as a possible diagnosis when a section showing chronic dermatitis is examined It often is a very difficult task to establish or rule out early mycosis

In subacute dermatitis, one sees spongiosis, intracellular edema and, usually also vesicle formation However, the vesicles are smaller than in acute dermatitis (Fig 25) Moderate acanthosis and varying degrees of parakeratosis are present. The inflammatory infiltrate in the dermis usually is pronounced and is composed of a multiplicity of cells: lymphocytes predominate, but neutrophils, eosinophils and

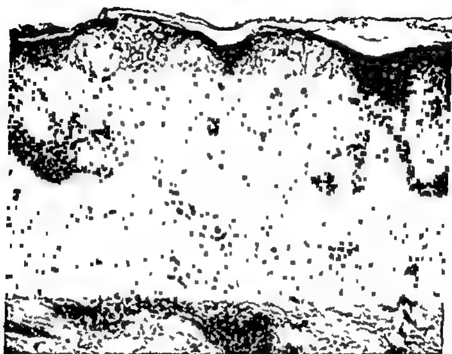


Fig 25 Subacute dermatitis nummular eczema There is intra epidermal vesicle formation The vesicles lie in areas formerly occupied by epidermal cells The epidermis shows parakeratosis and moderate acanthosis The dermis shows a perivascular infiltrate (×100)

histiocytes are also seen There may be considerable migration of neutrophils and lymphocytes through the epidermis

In chronic dermatitis, there is often marked acanthosis with elongation of the rete ridges There is hyperkeratosis intermingled with areas of parakeratosis Slight intercellular edema may be present in the epidermis, but vesicle formation is absent In the upper dermis, one sees a moderate amount of predominantly perivascular infiltration composed of various types of cells Lymphocytes prevail, but the number of eosinophils, histiocytes and fibroblasts may be considerable Neutrophils are absent The number of capillaries is increased and the walls of the arterioles and the small arteries may be thickened The term neurodermatitic reaction has been given by

that of psoriasis which shares with lichen simplex chronicus the tendency to elongation of the rete ridges However, psoriasis shows predominantly parakeratosis rather than hyperkeratosis thinning of the suprapapillary portions of the stratum malpighii edema of the upper portions of the papillae and not infrequently Munro micro abscesses Furthermore the papillary capillaries in psoriasis are di lated and tortuous whereas in lichen simplex chronicus they appear normal According to Stoughton and Wells the Hotchkiss McManus stain demonstrates the capillary changes in psoriasis very clearly and thus aids in its differentiation from lichen simplex chronicus

EXUDATIVE DISCOID AND LICHENOID CHRONIC DERMATOSIS (Sulz berger Garbe) The epidermis may show spongiosis and vesiculation as in subacute dermatitis or acanthosis with little or no edema as in chronic dermatitis The vessels of the upper dermis and the mid dermis are dilated and their walls thickened About them is a mantle of lymphocytes histiocytes polymorphonuclear neutrophils eosino- phils and numerous plasma cells Sachs and Kirsch state that the pres ence of many plasma cells gives the histologic picture a distinctive appearance so that the diagnosis can be established on microscopic findings alone

SEBORRHEIC DERMATITIS The histologic picture is not diagnostic It may be said to be halfway between psoriasis and chronic dermatitis The horny layer because of the tendency to desquamation is only poorly developed and most of its cells are parakeratotic The epi dermis shows slight to moderate acanthosis with elongation of the rete ridges and slight intracellular edema and spongiosis The dermis shows a mild chronic inflammatory infiltrate Munro micro abscesses and neutrophils migrating through the epidermis as seen in psoriasis occasionally are observed In cases in which the histologic picture resembles that of psoriasis the presence of spongiosis ser...

... the dermis Older lesions may show numerous newly formed capillaries embedded in a fibrotic dermis Whereas it has been assumed generally that venous and capillary stasis is responsible for the clinical manifestations of stasis derma titis Kulwin and Hines in a study of the vessels at the dermo-sub cutaneous junction found changes more often and more severely in the arterioles than in the venules The changes in both arterioles and venules consisted of intimal proliferation endothelial hyper plasia and medial hypertrophy Complete obliteration of arterioles

fungoides One should search for atypical histiocytes (so-called mycosis cells) mitotic figures clumping of nuclei karyorrhexis (disintegration of nuclei into nuclear dust) and *Pautrier micro abscesses* (For further details see page 485) However it should be realized that some atypicality of the histiocytes and an occasional mitotic figure sometimes may be seen in chronic dermatitis If in doubt, it is always best to request another specimen for histologic examination

A few words about the histologic aspects of the various members of the dermatitis eczema group are now in order

CONTACT DERMATITIS *Contact dermatitis* may be acute subacute or chronic The histologic descriptions given above for acute sub acute and chronic dermatitis apply in general to contact dermatitis Acute contact dermatitis presents numerous closely set large and small intra epidermal vesicles (Fig 24) Chronic contact dermatitis shows irregular acanthosis Even at that stage spongiosis and small intra epidermal vesicles are often present (Sachs Miller and Gray *1914* Miller)

NUMMULAR ECZEMA (infectious eczematoid dermatitis) This eruption characterized clinically by pinpoint vesicles usually shows histologically a picture of subacute dermatitis (Fig 25) In a moderately acanthotic epidermis one finds numerous scattered areas of intra epidermal vesiculation (Sachs Miller and Gray 1946) As a rule spongiosis about the vesicles is slight or absent

ATOPIC DERMATITIS (neurodermatitis disseminata) The histologic picture is usually that of a chronic dermatitis showing acanthosis with varying degrees of spongiosis The number of eosinophils in the inflammatory infiltrate is often considerable (Burkhart and Montgomery)

LICHEN SIMPLEX CHRONICUS (neurodermatitis circumscripta) The microscopic appearance is essentially that of a chronic dermatitis (Fig 26) There are hyperkeratosis interspersed with small areas of para keratosis acanthosis characterized by rather regular elongation of the rete ridges and elongation and broadening of the papillae There may be some spongiosis but vesiculation does not occur In addition to a chronic inflammatory infiltrate the dermis often shows a fair number of fibroblasts and some fibrosis even in the papillae

In the hypertrophic type of lichen simplex chronicus (lichenificatio gigantea or lichen corneus hypertrophicus) the epidermis shows in addition to acanthosis with elongation of the rete ridges considerable hyperkeratosis and papillomatosis (Shaffer and Beerman Hyman and Erger)

The histologic picture of lichen simplex chronicus may resemble

tion at first shows no evidence of lymphomatous infiltration in the dermis it is advisable to perform further biopsies at intervals (See also page 490)

DERMATOPATHIC LYMPHADENITIS

Any extensive dermatitis but particularly generalized exfoliative dermatitis whether due to lymphoma or not may cause a generalized lymphadenitis of the subcutaneous lymph nodes

Histopathology This lymphadenitis has certain characteristic histologic features not found in other types It was described first by Pautrier and Woringer as lipo-melanotic reticulosis Hurwitt introd [illegible] lymph [illegible] rminal centers The pulp of the lymph node shows considerable hyperplasia of reticulum cells Since the reticulum cells possess abundant and faintly eosinophilic cytoplasm the areas of reticular hyperplasia appear as large pale patches (Laipply) The reticulum cells show phagocytic activity and may contain hemosiderin melanin and, occasionally, fat The lymph follicles as well as the pulp of the lymph node are permeated with eosinophils neutrophils and plasma cells The intermediary sinuses are filled with reticulum cells (sinus catarrh) The melanin and the fat occasionally present in the lymph nodes originate in the skin and are carried into the lymphatics by scratching It has been suggested that the fat may not be sebum but ointment base (Bettley)

Differential Diagnosis These histologic changes differ from those observed in mycosis fungoides Hodgkin s disease and follicular lymphoma by the absence of destruction of the basic architecture of the lymph node the absence of Sternberg Reed cells and the presence of phagocytic activity in the reticulum cells (Hurwitt) The large lymph follicles present in dermatopathic lymphadenitis differ from those of follicular lymphoma by greater uniformity in size smaller number and absence of fissures which frequently separate the lymph follicles from the stroma in follicular lymphoma

In recent years the relationship of dermatopathic lymphadenitis to lymphoma has been discussed by several authors Some have assumed that a dermatopathic lymphadenitis can develop into lymphoma (Bluefarb and Webster) and others have regarded cases of generalized erythroderma with dermatopathic lymphadenitis as Brill Symmers disease (i e follicular lymphoma) even in the absence of the histologic criteria of follicular lymphoma (Rost) Neither point of view is justified Dermatopathic lymphadenitis as such is an en

was seen in specimens from ulcerated areas These authors concluded that arteriolar changes may be an important etiologic factor in stasis dermatitis

GENERALIZED EXFOLIATIVE DERMATITIS The histologic appearance may be that of a subacute or a chronic dermatitis In the subacute type there are parakeratosis marked intercellular and intracellular



FIG 27 Generalized exfoliative dermatitis due to arsphenamine There are parakeratosis marked intercellular and intracellular edema in the upper stratum malpighii acanthosis with elongation of the rete ridges and migration of inflammatory cells through the epidermis The upper dermis shows edema and a considerable amount of inflammatory infiltrate (×100)

edema, particularly in the upper stratum malpighii acanthosis with elongation of the rete ridges and migration of cells through the epidermis The upper dermis shows edema and a considerable amount of inflammatory infiltrate (Fig 27) If the edema in the upper stratum malpighii is pronounced the cells of the upper stratum may exfoliate together with the parakeratotic horny cells In the chronic type of exfoliative dermatitis the histologic picture is that of chronic dermatitis Each such case requires thorough histologic investigation in order to rule out lymphoma Montgomery has stated that 25 per cent of all cases of exfoliative dermatitis are proved on histologic examination to be associated with lymphoma Even if the histologic examina

Tzanck A. Le cytodiagnostic immédiat en dermatologie Ann dermat et syph 8 205 1948

Dermatitis Herpetiformis

Burkhart R. J and Montgomery H Dermatologic significance of tissue eosinophilia Arch Dermat & Syph 49 19 1944
Civatte A Diagnostic histopathologique de la dermatite polymorphe douloureuse ou maladie de Duhring Brocq Ann dermat et syph 3 1 1943
Lapière M A propos du diagnostic différential du pemphigus chronique vulgaire et de la dermatite polymorphe de Duhring Brocq Arch belges dermat et syph 1 216 1939

Erythema Multiforme

Costello M J Erythema multiforme exudativum J Invest Dermat 8 127 1947
Winer L. H and Lipschultz C. E Comparative study of histology and cytology in vesiculating eruptions Arch Dermat & Syph 65 270 1952

Burn

Moritz A R Studies of thermal injury III The pathology and pathogenesis of cutaneous burns Am J Path 23 915 1947

tirely nonspecific reaction to an extensive dermatitis Since lymphoma may manifest itself as an extensive dermatitis (see page 490), it can cause a dermatopathic lymphadenitis Subsequently, the lymphoma may extend to lymph nodes previously affected by dermatopathic lymphadenitis, but in that case the latter is only chronologically—not etiologically—the forerunner of the lymphoma (Jarrett and Kellett; Keller and Staemmler)

MILIARIA

Miliaria occurs following excessive sweating in parts of the body covered by clothing There are two types *miliaria crystallina* and *miliaria rubra* In miliaria crystallina, asymptomatic, small, superficial, noninflammatory vesicles are present In miliaria rubra, the lesions consist of pruritic, discrete but closely aggregated papules papulovesicles and vesicles surrounded by erythema

The cause of miliaria lies in excessive hydration of the horny layer by sweat This results in swelling of the keratin, closure of the narrow sweat pores by keratin and retention of sweat in the sweat ducts

Histopathology. In miliaria crystallina, histologic examination reveals occlusion of the orifices of sweat ducts by keratin plugs and distention of the sweat ducts within the epidermis and, occasionally, also in the dermis Intracorneal vesicles are present There is no inflammatory infiltrate Evidence in favor of the assumption that the intracorneal vesicles contain sweat are the observations in experimental miliaria crystallina by Shelley and Horvath that the vesicles on serial sections proved to be in direct communication with sweat ducts and failed to form when sweating was inhibited by the local injection of atropine

In miliaria rubra an inflammatory infiltrate is present around the sweat ducts in the epidermis and the upper dermis Either an intraepidermal or a subepidermal vesicle is seen It appears that in severe cases of miliaria rubra, which are associated with thermogenic anhidrosis, the sweat duct ruptures either within the epidermis leading to an intra epidermal vesicle or at the epidermal dermal junction leading to a subepidermal vesicle (O Brien, Sulzberger, Zimmerman and Emerson) On the other hand, in mild cases the sweat duct does not break, as a rule, but sweat merely escapes from the sweat duct into the epidermis leading to the formation of an intra epidermal "spongiotic" vesicle (Sulzberger and Zimmerman)

POMPHOLYX (DYSHIDROTIC ERUPTION)

This is a recurrent eruption of numerous deep seated vesicles occurring singly and in groups on the palms and the soles Inflam

Tzanck, A.· Le cytodiagnostic immédiat en dermatologie. Ann dermat. et syph. 8 205, 1948

Dermatitis Herpetiformis

Burkhart, R J, and Montgomery, H. Dermatologic significance of tissue eosino- [illegible]

Civa [illegible] · dou

Lap [illegible] vul gaire et de la dermatite polymorphe de Duhring Brocq Arch belges dermat et syph 1 216 1939

Erythema Multiforme

Costello, M J Erythema multiforme exudativum J Invest Dermat 8 127, 1947

Winer L. H, and Lipschultz C E Comparative study of histology and cytology in vesiculating eruptions Arch Dermat & Syph 65 270, 1952

Burn

Moritz A R Studies of thermal injury III The pathology and pathogenesis of cutaneous burns Am J Path 23 915 1947

8

Noninfectious Inflammatory Diseases

URTICARIA

Urticaria is characterized by the presence of transient edematous macules or wheals, and is accompanied by considerable itching

Histopathology. An urticarial wheal shows edema, particularly of the upper dermis The collagen bundles as well as the individual *fibers are separated by edema.* The collagenous substance appears swollen and stains poorly. In early wheals, i e , those only a few min *utes old, one finds either no inflammatory reaction or merely a* slight perivascular infiltrate composed of lymphocytes. Wheals an



Fig 39 Prurigo nodularis. There are hyperkeratosis and ... of the epidermis approach

four old or older show a mild or even moderately severe lymphocytic infiltrate around the capillaries (Torok and Lehner)

PRURIGO NODULARIS

In one usually chiefly

Histopathology One observes pronounced hyperkeratosis and acanthosis There may be deep invaginations of the horny layer The ... dermis ma

ERYTHEMA NODOSUM

The lesions consist of tender red or livid red nodes which are slightly raised above the level of the skin They vary from 1 to 5 cm in diameter and usually are limited to the anterior surfaces of the legs they may however occur elsewhere They involute within a few weeks without breaking down

Histopathology The histologic changes are located mainly in the upper portion of the subcutaneous tissue The dermis merely shows a moderate amount of perivascular infiltrate composed predominantly of lymphocytes

In early lesions one observes in the upper portion of the subcutaneous tissue a scattered infiltrate consisting mainly of neutrophils and lymphocytes Some histiocytes and occasionally eosinophils are present but plasma cells are absent The inflammatory infiltrate extends as the disease progresses both upward toward the fatty tissue

irregular outline No abscess formation or necrosis occur

The blood vessels especially the veins may show severe involvement so that many authors believe that a vasculitis represents the primary and predominant lesion (Rotnes Grzybowski) Other authors however state that the blood vessels are not necessarily affected severely and may show only mild involvement (Pautrier and Woringer Lofgren and Wahlgren) In cases with vascular changes one observes especially in the larger veins invasion of the vascular

walls by the inflammatory infiltrate and marked endothelial proliferation (Fig 40) However, complete occlusion and thrombosis are rare

Epithelioid and giant cells are absent in early lesions However occasionally one finds small nodules composed of histiocytes lying either in radial arrangement or in palisade like arrangement around

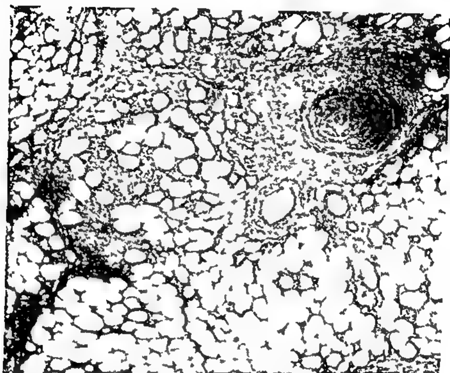


Fig 40 Erythema nodosum A nonspecific inflammatory infiltrate extends in small scattered patches through the subcutaneous fat A large subcutaneous vein shows endothelial proliferation and invasion of its wall by inflammatory cells (×50)

a small central fissure (Fig 41) (Miescher) Not infrequently these nodules are permeated by neutrophils Since they are found in no other disease they are of considerable diagnostic value (Nubé)

Older lesions show fewer neutrophils and more lymphocytes than young lesions Often giant cells are present at this stage The giant cells usually of the foreign body type may be found outside of or within foci of epithelioid cells In the latter case the arrangement simulates that found in tuberculosis (Rotnes) However caseation is always absent

Differential Diagnosis For differentiation from erythema induratum see page 186 In cases of erythema nodosum showing severe vascular involvement periarteritis nodosa must be excluded In the

latter disease however the arteries are predominantly involved one observes necrosis of vascular walls and the infiltrate usually contains a large percentage of eosinophils Nodular vasculitis greatly resembles the late stage of erythema nodosum It differs from erythema nodosum by showing a larger degree of vascular involvement including in

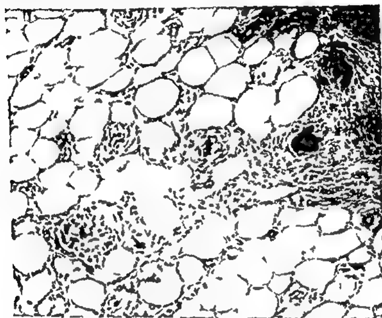


Fig 41 Erythema nodosum An older lesion shows two small nodules composed of histiocytes and to the right several giant cells of the foreign body type (×200)

volvement of vessels of large caliber However it is possible that it represents a variant of erythema nodosum

NODULAR VASCULITIS

Clinically this disease is characterized by slightly painful nodules occurring chiefly on the legs They generally persist for

... iterative changes in both veins and arteries (Fig 42) In addition one observes ...

Irgang) ... (Woodburne and Philpott

walls by the inflammatory infiltrate and marked endothelial proliferation (Fig. 40). However, complete occlusion and thrombosis are rare.

Epithelioid and giant cells are absent in early lesions. However, occasionally one finds small nodules composed of histiocytes lying either in radial arrangement, or in palisade like arrangement around

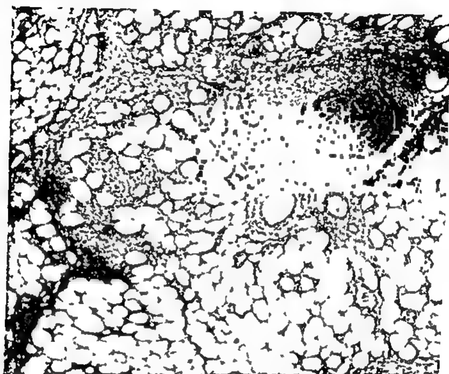


FIG 40 Erythema nodosum. A nonspecific inflammatory infiltrate extends in small, scattered patches through the subcutaneous fat A large subcutaneous vein shows endothelial proliferation and invasion of its wall by inflammatory cells (×50)

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Older lesions show fewer neutrophils and more lymphocytes than young lesions. Often, giant cells are present at this stage The giant cells, usually of the foreign-body type, may be found outside of, or within foci of, epithelioid cells. In the latter case, the arrangement simulates that found in tuberculosis (Rotnes). However, caseation is always absent.

Differential Diagnosis. For differentiation from erythema induratum, see page 186 In cases of erythema nodosum showing severe vascular involvement, periarteritis nodosa must be excluded. In the

is absent

The stratum malpighii is thinned above the papillae, often to only two or three layers of cells The rete ridges show considerable elongation They often are slender in their upper portion and thickened in



Fig 43 Psoriasis Low magnification There is parakeratosis The rete ridges are elongated and thickened in their lower portion There are edema and clubbing of the papillae (×50)

their lower portion They may show branching at their bases, causing

may be found scattered through the stratum malpighii

Corresponding to the elongation and the branching of the rete ridges the papillae are elongated and tortuous The upper part of the papillae is edematous and club shaped The capillaries in the papillae are dilated and tortuous and show slight thickening of their walls These changes in the capillaries can be demonstrated best by the use of the Hotchkiss McManus stain (Stoughton and Wells). A mild to moderately severe inflammatory infiltrate is present in the upper dermis, particularly in the papillae It consists of lymphocytes

It is probable that nodular vasculitis is a variant of *erythema nodosum*. For their differential diagnosis see under *erythema nodosum*, see page 97.



Fig. 42. Nodular vasculitis. The wall of a large subcutaneous vein is greatly thickened and infiltrated with inflammatory cells. The lumen is obliterated (×50)

PSORIASIS

Psoriasis is a chronic disorder characterized by dull red or brownish papules and plaques. The lesions are sharply demarcated, dry and usually covered with layers of fine silvery scales. As the scales are removed by gentle curettage, one frequently sees characteristic fine *bleeding points. In severe cases, the disease may affect the entire skin* and present the clinical picture of generalized exfoliative dermatitis (exfoliative psoriasis).

Histopathology. Histologically, psoriasis is characterized by (1) parakeratosis, (2) *thinning of the suprapapillary portions* of the stratum malpighii, (3) elongation of the rete ridges, (4) edema and clubbing of the papillae and (5) Munro micro-abscesses (Fig. 43).

Corresponding to the layered silvery scaling observed clinically, the horny layer is considerably thickened and consists predominantly of parakeratotic cells, arranged in lamellae with air spaces in between.

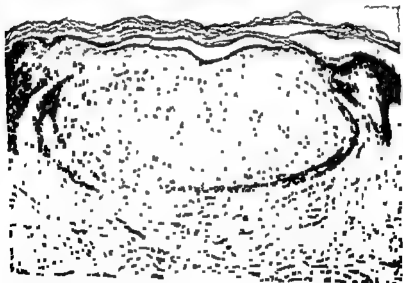
edema of the rete cells overlying the papillae and (4) capillary dilatation in the tips of the papillae

EXFOLIATIVE PSORIASIS The histologic picture of exfoliative psoriasis may still show enough of the characteristics of psoriasis to allow this diagnosis Frequently however the appearance is indistinguishable from that of exfoliative dermatitis due to other causes

Differential Diagnosis The histologic picture of psoriasis may resemble that of lichen simplex chronicus For their differentiation, see page 73 Differentiation from seborrheic dermatitis is not always possible Seborrheic dermatitis may show all the features of psoriasis, though less pronounced than in psoriasis In addition however, one finds a fair degree of spongiosis which in psoriasis is either very slight or absent

PUSTULOSIS PALMARIS ET PLANTARIS (PUSTULAR PSORIASIS PUSTULAR BACTERID)

Two diseases have been described in the literature under the name of pustular psoriasis generalized pustular psoriasis and pustular



Pustulosis palmaris et plantaris (pustular bacterid) A large intraepidermal unilocular pustule containing many neutrophils is present (×100)

psoriasis of the palms and the soles Neither of them however, is a form of psoriasis Actually, pustular lesions do not occur in psoriasis

So-called generalized pustular psoriasis is identical with the gen

and histiocytes, except in early lesions which, in addition, show polymorphonuclear leukocytes in the infiltrate. Plasma cells are found only rarely and eosinophils hardly ever

The Munro micro abscesses (Fig. 44) are located either in the stratum corneum or directly beneath it They represent small ac-



Fig 44 Psoriasis High magnification of Figure 43 A Munro micro abscess (M) is located within the parakeratotic horny layer The supra papillary portions of the stratum malpighii are thinned and show intra cellular edema Intercellular edema, however is absent The capillaries in the tips of the papillae are dilated (×200)

cumulations of neutrophils which have migrated there through the epidermis Munro micro abscesses, as a rule, are found easily in early lesions In older lesions, they are few in number or even absent Thus, their absence does not rule out psoriasis Neither does their presence establish a diagnosis of psoriasis, since Munro micro abscesses may occur also in seborrheic dermatitis, acrodermatitis continua (Hallopeau), keratosis blennorrhagica and parapsoriasis guttata.

The bleeding points which may be produced by gentle scraping of the skin correspond to the apices of papillae They are due to the following histologic changes (1) parakeratosis, (2) thinning of the stratum malpighii above the tips of the papillae, (3) intracellular

walls thus form a sponge like network in the interstices of which neutrophils continue to accumulate (Fig 46) As the pustule ages the cellular walls gradually break in the center of the pustule so that

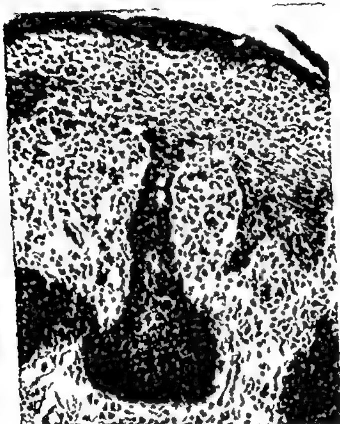


Fig 46 Acrodermatitis continua of Hallopeau There is acanthosis with elongation of the *rete ridges* The upper stratum malpighii contains a *spongiform pustule* the cellular walls of the edematous *squamous cells* form a sponge like net work in the interstices of *which neutrophils* have accumulated (×300)

a large cavity forms At the periphery of the pustule however, the network persists for a *much longer* time

Differential Diagnosis. The *spongiform* pustule of Kogoj represents a striking histologic lesion and is *characteristic* of acrodermatitis continua However it is not diagnostic of that disease since it occurs also in three other *diseases* *impetigo* herpetiformis *keratosis* blennorrhagica and Reiter's disease Differentiation of *these* four

eralized form of acrodermatitis continua (Lapiere, Bruck) and will be described there (see below)

Pustular psoriasis of the palms and the soles, a term introduced by Barber, is a misnomer This disease is now referred to frequently as either pustular bacterid (Andrews) or acrodermatitis pustulosa (Sachs, MacKee and Rothstein) The term pustulosis palmaris et plantaris is preferable, however

Pustulosis palmaris et plantaris is a chronic, indolent disorder limited to the palms and the soles and characterized by the appear ance of crops of deep seated pustules within areas of erythema and scaling

Histopathology. The histologic picture does not resemble that of psoriasis A large, intra epidermal, unilocular pustule is present (Fig 45) It contains many neutrophils and disintegrated cellular elements The epidermis surrounding the pustule shows slight acanthosis with little or no spongiosis In the dermis underlying the pustule, a mod erately severe inflammatory infiltrate is present, composed mainly of lymphocytes and histiocytes but containing also a few neutrophils Histologic features of psoriasis, such as parakeratosis elongation of the rete ridges, thinning of the suprapapillary portions of the stratum malpighii and dilatation of the papillary capillaries are always absent (Sachs and Scannone, Sachs, MacKee and Rothstein)

ACRODERMATITIS CONTINUA
(Hallopeau)

Acrodermatitis continua of Hallopeau, a chronic disease having pustules as a primary lesion, usually is limited to the hands and the feet The distal portions of the fingers and the toes are predomi nantly involved Occasionally, however, the disease is generalized The affected areas are dark red, dry, shiny and scaling and are studded with shallow pustules Lesions located on the distal portions of the fingers and the toes may cause atrophy of the skin and loss of nails

Histopathology. The epidermis shows parakeratosis and moderate acanthosis with elongation of the rete ridges An inflammatory in filtrate containing many neutrophils but few or no eosinophils is present in the dermis Many neutrophils are seen invading the epidermis

However, the characteristic lesion consists of the so called spongi form pustule of Kogoj This type of pustule forms in the uppermost stratum malpighii through the migration of neutrophils into edema tous squamous cells This invasion causes disintegration of the cyto plasm and of the nucleus but not of the cellular walls The cellular

walls thus form a sponge like network in the interstices of which neutrophils continue to accumulate (Fig 46) As the pustule ages, the cellular walls gradually break in the center of the pustule so that

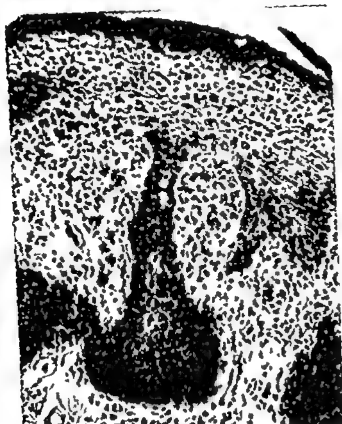


Fig 46 Acrodermatitis continua of Hallopeau There is acanthosis with elongation of the rete ridges The upper stratum malpighii contains a spongiform pustule the cellular walls of the edematous squamous cells form a sponge like net work in the interstices of which neutrophils have accumulated (×300)

a large cavity forms At the periphery of the pustule however, the network persists for a much longer time

Differential Diagnosis The spongiform pustule of Kogoj represents a striking histologic lesion and is characteristic of acrodermatitis continua However, it is not diagnostic of that disease since it occurs also in three other diseases impetigo herpetiformis, keratosis blennorrhagica and Reiter's disease Differentiation of these four

diseases may be impossible However, in impetigo herpetiformis, the infiltrate contains, as a rule, a large number of eosinophils (see below). Older lesions of keratosis blennorrhagica and Reiter's dis ease often can be differentiated from acrodermatitis continua by the presence of a greatly thickened horny layer (see page 172)

IMPETIGO HERPETIFORMIS

This rare, usually fatal, disease is seen mainly in pregnant women and occasionally in hypoparathyroidism It is characterized by the presence of pustules set in groups or in circinate arrangement on erythematous patches

Histopathology. The histologic picture, like that of acrodermatitis continua, is characterized by the presence of the spongiform pustule (Kogoj) (See "Acrodermatitis Continua" for a description of the spongiform pustule) The dermal infiltrate as well as the pustule contain a conspicuous number of eosinophils (Rost)

Differential Diagnosis. The presence of many eosinophils aids in the differentiation of impetigo herpetiformis from the other three diseases with spongiform pustules acrodermatitis continua, keratosis blennorrhagica and Reiter's disease The latter two diseases, in addition, often show conspicuous hyperkeratosis in their older lesions

PARAPSORIASIS

Parapsoriasis comprises a group of rare dermatoses Three of the four forms of parapsoriasis are characterized by an asymptomatic maculopapular eruption of slow evolution and marked chronicity These forms are parapsoriasis guttata, parapsoriasis lichenoides (parakeratosis variegata) and parapsoriasis en plaques In parapsoriasis guttata, one observes especially on the trunk numerous papules which may or may not be covered with fine scales In parapsoriasis lichenoides, papules generally are distributed in a netlike arrangement In parapsoriasis en plaques, well defined patches and plaques of various size and shape occur The fourth form of parapsoriasis parapsoriasis varioliformis of Habermann, also called pityriasis lichenoides et varioliformis acuta differs from the previously mentioned forms by running an acute course terminating in from a few weeks to several months The eruption consists of vesicles, papules and papulonecrotic lesions terminating in varioliform scars

Histopathology. None of the four forms of parapsoriasis shows a diagnostic histologic picture Parapsoriasis guttata, parapsoriasis lichenoides and parapsoriasis en plaques show the histologic picture of chronic dermatitis, while parapsoriasis varioliformis shows an acute inflammatory process with foci of necrosis

the infiltrate in the manner of a claw clutching a ball

The cause of the disease is not known Ellis and Hill regard lichen nitidus as closely related to lichen planus because they found that the two diseases may occur together and histologic sections obtained from patients with lichen planus may show lichen nitidus like lesions

LICHEN STRIATUS

Lichen striatus is an uncommon eruption which as a rule occurs in children It manifests itself usually on the extremities as a long band composed of small lichenoid papules The eruption appears suddenly and involutes within a few weeks or months Itching is absent

Histopathology The histologic changes are similar to those of neurodermatitis circumscripta In some cases the chronic inflammatory infiltrate is more markedly perivascular than in neurodermatitis circumscripta and surrounds the vessels of the upper dermis as densely packed mantles (Senear and Caro Pinkus)

PITYRIASIS RUBRA PILARIS

The primary lesions are reddish follicular papules They gradually coa[illegible] tes Ultimately most of t[illegible] late stage however foll[illegible] ecially on the dorsa of the fingers

Histopathology The essential pathologic process is follicular hyperkeratosis In addition there is diffuse hyperkeratosis with spotted parakeratosis The epidermis shows irregular acanthosis usually of mild degree There often is liquefaction degeneration of the basal cells (Brunsting and Sheard) In the upper dermis a mild chronic inflammatory infiltrate is observed around the blood vessels

Differential Diagnosis For a differential diagnosis from phrynoderma (vitamin A deficiency) see page 286

GRANULOMA FACIALE (EOSINOPHILIC GRANULOMA OF THE FACE)

This disorder only recently established as a disease entity consists of soft purplish slowly growing and asymptomatic patches limited to the face Except for prominence of the follicular openings the surface of the skin appears normal

Histopathology. A dense, granulomatous infiltrate is located mainly in the upper half of the dermis (Fig 52) Quite characteristically, the infiltrate does not invade the epidermis or the pilosebaceous appendages but is separated from them by a narrow zone of normal collagen The pilosebaceous appendages are well preserved. Two stages can be differentiated in the development of the

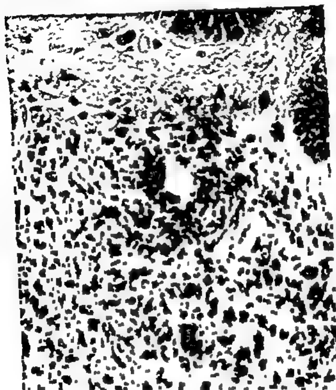


Fig 52 Granuloma faciale A dense infiltrate containing many eosinophils is present in the dermis The infiltrate does not invade the epidermis or the sebaceous gland shown on the right but is separated from them by a zone of normal collagen (×100)

infiltrate, an early "leukocytic" and a late "fibrotic" stage The two stages may occur together in the same lesion

In the early "leukocytic" stage, eosinophils predominate, but neutrophils and histiocytes are found in large number and, in addition, a few lymphocytes, plasma cells and mast cells The infiltrate thus has a polymorphous appearance The capillaries are dilated and surrounded by degenerated collagen (Fig 53) In some cases considerable amounts of hemosiderin are present in the upper dermis within and outside of histiocytes (Lever, Lane, Downing and Spangler). The presence of foam cells has been described in one case (Lever).

In the late "fibrotic" stage, the infiltrate is broken up into variously sized patches by strands of collagen. The number of eosinophils and neutrophils is greatly reduced, and plasma cells, lymphocytes and fibroblasts predominate. The capillaries often have fibrotic walls.



...trate which is densest around a dilated capillary. Two types of cells, eosinophils and histiocytes, predominate. (×400)

Differential Diagnosis. The arrangement and the composition of the infiltrate in granuloma faciale result in a diagnostic histologic picture with no resemblance to that of eosinophilic granuloma with which the disease was at first confused (Lever). Although eosinophilic granuloma, which represents an abortive form of Hand Schuller Christian disease (see page 265), also contains many eosinophils and histiocytes, its histologic appearance differs from that of granuloma faciale by the follow...

larger and ...

lie in patch...

the epidermis (Lever and Leeper) For a differentiation from erythema elevatum diutinum, see below

ERYTHEMA ELEVATUM DIUTINUM

This rare disorder shows persistent, red to purple nodules with some tendency to grouping about the joints, especially on the dorsa of the hands, the wrists and the elbows The nodules at first are soft but later, due to fibrous transformation, become hard

Histopathology. Erythema elevatum diutinum has a fairly diagnostic histologic picture which was first described by Weidman and Besancon, and then by Ketron and by Weiss as well as by others The disease described in 1894 by Crocker and Williams as erythema elevatum diutinum of the Bury type is now widely regarded as a variant or late stage of granuloma annulare (Haber and Russell)

Erythema elevatum diutinum, in its early stage, shows a dense, predominantly perivascular infiltrate composed largely of neutrophils intermingled with some lymphocytes and histiocytes In most cases, a peculiar hyaline degeneration of the reticulum fibers around the capillaries has been observed This degeneration has been referred to by Weidman and Besancon and by Ketron as formation of "toxic hyalin" This toxic hyalin has a smooth, glassy appearance and stains intensely pink with eosin

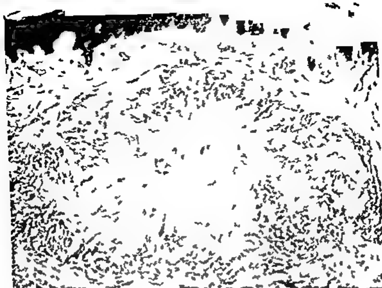
In the late, fibrous stage, the cellular infiltrate is much less pronounced and extensive fibrosis is present The capillaries may still show their mantle of toxic hyalin or may merely show fibrous thickening (Ketron)

Differential Diagnosis The histologic appearance of erythema [illegible] by the [illegible] sence of a zone of normal collagen beneath the epidermis and the presence of "toxic hyalin" about the capillaries

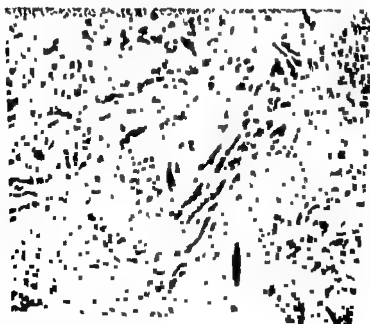
GRANULOMA ANNULARE

The lesions which are found most commonly on the hands and the feet, consist of small, firm, pale red nodules which tend to be [illegible] ngement The disease is chronic [illegible]

[illegible] anuloma annulare is character ized by focal degeneration of the collagen in the dermis deposits of mucin between the degenerated collagenous bundles and reactive inflammation and fibrosis The degeneration of collagen within the foci may be complete or incomplete Some cases show foci of both complete and incomplete degeneration and others show only one



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large focus of complete collagen degeneration In the majority of cases however one finds multiple foci of incomplete degeneration without any foci of complete degeneration

In foci of complete degeneration one finds a sharply demarcated area of coagulation necrosis surrounded by an infiltrate of histiocytes fibroblasts and lymphocytes in a radial arrangement (Fig 54)

In foci of incomplete degeneration one finds ill defined areas in which collagen fibers are found in various stages of degeneration ranging from mild homogenization and fragmentation to granular degeneration and coagulation necrosis A considerable amount of the collagen in such areas may appear normal Lymphocytes histiocytes and fibroblasts infiltrate between the partially degenerated collagen fibers and new collagen is being laid down Thus the affected areas of the dermis present a completely disorderly arrangement of the collagen bundles (Fig 55)

In both types of collagen degeneration though more frequently in areas of incomplete degeneration fine threads and granules of mucin are deposited between the degenerated collagen bundles The mucin stains light blue with routine stains and red when Best s mucicarmine stain is used (See Plate 1)

In areas of collagen degeneration the elastic tissue shows fragmentation and may be largely destroyed In some areas there may even be greater destruction of elastic than of connective tissue A moderate or even considerable amount of lymphocytic infiltration is found around the blood vessels outside the areas of degeneration The walls of the blood vessels show no pathologic changes however except occasional mild endothelial proliferation In some cases a few giant cells of the foreign body type are present They usually are situated near the periphery of the infiltrate and are not associated with any zone of necrosis (Prunty and Montgomery)

Differential Diagnosis The type of granuloma annulare showing multiple foci of incomplete collagen degeneration may greatly resemble necrobiosis lipoidica which shows this same pattern of collagen degeneration (see page 269) However necrobiosis lipoidica differs from granuloma annulare by the presence of vascular changes of lipid material and of many foreign body giant cells and by the absence of mucin

The type of granuloma annulare showing one or several large foci of complete collagen degeneration may be almost indistinguishable from the subcutaneous nodes of rheumatoid arthritis (see below) However in the nodes of rheumatoid arthritis the areas of degen

the dermis

red cellular

eaction, mainly histiocytes and fibroblasts, while in granuloma an ıulare there are, in addition, many lymphocytes (Bowess)

SUBCUTANEOUS NODULES OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

In both rheumatic fever and rheumatoid arthritis, small firm nodules may form in the subcutaneous tissue The commonest sites



Fig 56 Subcutaneous nodule of rheumatoid arthritis There is a large central zone of necrosis surrounded by histiocytes in palisade arrangement (×100)

are about the elbows, the knees and the ankles Their size varies from a few millimeters to 2 cm

Histopathology The subcutaneous nodules found in these two diseases are similar in many of their pathologic features In both diseases they are composed of three reasonably well-defined zones (1) a central zone, or zone of necrosis, (2) an intermediate zone, comprising proliferating histiocytic cells and (3) a peripheral zone, consisting of chronic inflammatory cells (Bennett, Zeller and Bauer) However, exudative changes prevail in the nodules of rheumatic fever, proliferative and necrotic changes in those of rheumatoid arthritis

large focus of complete collagen degeneration In the majority of cases, however, one finds multiple foci of incomplete degeneration without any foci of complete degeneration

In foci of complete degeneration, one finds a sharply demarcated area of coagulation necrosis surrounded by an infiltrate of histiocytes, fibroblasts and lymphocytes in a radial arrangement (Fig 54)

In foci of incomplete degeneration, one finds ill defined areas in which collagen fibers are found in various stages of degeneration *ranging from mild homogenization and fragmentation to* granular degeneration and coagulation necrosis A considerable amount of the collagen in such areas may appear normal Lymphocytes, histiocytes and fibroblasts infiltrate between the partially degenerated collagen fibers and new collagen is being laid down Thus, the affected areas of the dermis present a completely disorderly arrangement of the collagen bundles (Fig 55)

In both types of collagen degeneration, though more frequently in areas of incomplete degeneration, fine threads and granules of mucin are deposited between the degenerated collagen bundles The mucin stains light blue with routine stains and red when Best s mucicarmine stain is used (See Plate 1)

In areas of collagen degeneration, the elastic tissue shows fragmentation and may be largely destroyed In some areas, there may even be greater destruction of elastic than of connective tissue A moderate or even considerable amount of lymphocytic infiltration is found around the blood vessels outside the areas of degeneration The walls of the blood vessels show no pathologic changes, however, except *occasional mild endothelial proliferation In some cases,* a few giant cells of the foreign body type are present They usually are situated near the periphery of the infiltrate and are not associated with any zone of necrosis (Prunty and Montgomery)

Differential Diagnosis The type of granuloma annulare showing multiple foci of incomplete collagen degeneration may greatly resemble necrobiosis lipoidica which shows this same pattern of collagen degeneration (see page 269) However, necrobiosis lipoidica differs from granuloma annulare by the presence of vascular changes, of lipid *material and of many foreign body* giant cells and by the absence of mucin

The type of granuloma annulare showing one or several large foci of complete collagen degeneration may be almost indistinguishable from the subcutaneous nodes of rheumatoid arthritis (see below) However, in the nodes of rheumatoid arthritis the areas of degeneration are usually larger, they are more deeply located in the dermis or even in the subcutis, and *they are encircled* by a less varied cellular

After many years' duration, an atrophic stage may be reached in which the findings are no longer diagnostic, since one sees merely an atrophic epidermis and an atrophic, fibrotic dermis without inflammatory infiltrate.



FIG 57 Acrodermatitis chronica atrophicans There is atrophy of the stratum malpighii A bandlike infiltrate is separated from the epidermis by a narrow zone of normal collagen The dermis shows interstitial edema and atrophy of the collagen bundles. Because of this atrophy, the thickness of the dermis is markedly decreased and the sweat glands lie unusually close to the epidermis (×100)

The bandlike areas of fibrosis resembling scleroderma and the [illegible] able from that of scleroderma

RADIODERMATITIS

An early (acute) and late (chronic) stage of radiodermatitis are recognized The early stage occurs within a few days after adminis

In rheumatic fever, the central zone shows "fibrinoid degeneration" (For a discussion of fibrinoid degeneration, see "Acute Systemic Lupus Erythematosus," page 297) The intermediate zone is composed of edematous collagen infiltrated with inflammatory cells, including many large *mononuclear cells (histiocytes)* which resemble the predominant cells of myocardial Aschoff nodules

In rheumatoid arthritis, the central zone shows necrosis of all preexisting collagen, and the intermediate zone distinct palisading of histiocytes and fibroblasts around the central zone of necrosis (Fig 56)

Differential Diagnosis. For differentiation of the nodules of rheumatoid arthritis from granuloma annulare, see 'Granuloma Annulare," page 116

ACRODERMATITIS CHRONICA ATROPHICANS

This condition affects the extremities The skin presents a bluish red or a brownish, atrophic, wrinkled appearance Fine scaling is usually present Because of decrease in the amount of subcutaneous fat, the subcutaneous veins are clearly visible In some cases, bandlike areas of fibrosis, resembling scleroderma, and fibrous nodules are observed, especially along the ulna as "ulnar bands" and along the tibia

Histopathology. The histologic picture is characteristic One observes mild to moderate hyperkeratosis and atrophy of the epidermis, with absence of the rete ridges Just beneath the epidermis, there is a narrow zone of connective tissue separating a dense band of inflammatory infiltrate from the epidermis In addition to this bandlike infiltrate, one finds scattered areas of inflammatory infiltration throughout the dermis, particularly around the blood vessels The infiltrate is composed predominantly of lymphocytes, but also contains histiocytes Chromatophores laden with melanin or hemosiderin may be present The entire dermis shows interstitial edema and atrophy of the collagenous bundles The atrophy results in a gradual decrease of the dermis to a half or a quarter of its normal thickness (Fig 57)

The sebaceous glands and the hairs undergo atrophy early in the disease and usually are entirely absent However, the sweat glands are, as a rule, preserved Because of the thinness of the dermis they lie unusually close to the epidermis The blood vessels are dilated and may show *endothelial proliferation*

The subcutaneous tissue shows decided atrophy The fat cells vary in size and are irregular in shape Foci of inflammatory infiltration and a varying degree of fibrosis are present

changes An inflammatory infiltrate is seen throughout the dermis, especially about the appendages The blood vessels are dilated and reveal edema of their walls and endothelial proliferation The collagen bundles show edema and homogenization In severe cases, the



FIG 59 Late radiodermatitis The vessels (V) show

epidermis and the upper dermis undergo *necrosis* The area of necrosis is invaded and surrounded by polymorphonuclear leukocytes

Histopathology of Late (Chronic) Radiodermatitis. The epidermis is irregular showing atrophy in some areas and acanthosis with hyperkeratosis in others The *rete* cells frequently show atypicality, such as disorderly arrangement, individual cell dyskeratosis and an increased number of mitotic figures Thus the changes may resemble those of Bowen's disease (intra-epidermal squamous-cell carcinoma) In addition there often is irregular downward growth of the epidermis The

tration of a massive dose of roentgen rays or radium. At first, there is erythema, which is followed by desquamation and pigmentation. If the dose administered is sufficiently large, ulceration will ensue. The late (chronic) stage of radiodermatitis occurs from a few months



FIG. 58. Late radiodermatitis. The epidermis shows acanthosis and downward growth around a telangiectatic blood vessel. Many irregularly dilated lymphatics are located directly beneath the epidermis. The collagen shows degeneration. (×100)

to several years after the administration of large amounts of roentgen rays or radium. The skin shows atrophy with interspersed areas of hyperkeratosis, irregular hyperpigmentation, telangiectases and loss of hair. Ulceration may be present. The hyperkeratoses may develop into squamous cell carcinoma.

Histopathology of Early (Acute) Radiodermatitis. The cells of the epidermis, particularly those of the basal layer, are hydropic and their nuclei show pyknosis. The epithelial cells of the hair follicles, the sebaceous glands and the sweat glands may show similar degenerative

Histopathology The histologic appearance usually is that of a nonspecific chronic dermatitis (see page 70) However the erythematous lesions frequently present areas of liquefaction degeneration of the basal layer and edema together with a patchy predominantly lymphocytic infiltrate in the upper dermis Differentiation from lupus erythematosus may then be impossible However in some cases of solar dermatitis a moderate number of eosinophils is present in the infiltrate Since eosinophils are generally not observed in lupus erythematosus their presence aids greatly in the differentiation of the two diseases (Lamb)

HIDROCYSTOMA

This condition is characterized by the presence on the face of numerous clear tense deep-seated vesicles varying in size from a few millimeters to 1 centimeter

Histopathology On histologic examination one observes in the dermis large cystic cavities lined by epithelial cells which usually are arranged in two layers Small papillary projections into the lumina of the cysts have been described (Kenedy and Lehner)

Most authors regard the cysts as caused by retention of sweat in the dermal portion of eccrine sweat ducts However Kenedy and Lehner believe that the cysts are not merely the result of retention of sweat and passive dilatation of the excretory ducts but are due to a proliferation of the excretory duct epithelium which leads to occlusion of the ducts

ACNE VULGARIS

Acne vulgaris a disease occurring predominantly in puberty affects the face the upper chest and the upper back The primary lesion is the comedo As a foreign body reaction to the comedo and due to secondary infection follicular papules and pustules and subcutaneous abscesses may occur

Histopathology Histologically acne vulgaris represents a perifolliculitis occurring around a comedo Comedones are composed of sebum and keratotic as well as parakeratotic cells and are located in the pilosebaceous follicles

In the early acne lesion one finds an infiltrate of lymphocytes and plasma cells around a comedo-filled pilosebaceous follicle together with atrophy and fragmentation of sebaceous glands The atrophy and the fragmentation of sebaceous glands probably are due to the stasis and the pressure caused by the comedo within the follicle The fragmentation of sebaceous glands in turn causes an inflammatory reaction (Lynch) Occasionally foreign body giant cells are found in

rete ridges may grow around telangiectatic vessels, which may thus become completely enclosed in the epidermis (Fig 58).

In the dermis, the collagenous fibers are swollen and sclerotic In some areas, they are broken apart and stain basophilic Formation of new, young connective tissue is found throughout the dermis, but especially around the blood vessels Directly beneath the epidermis, one often sees numerous irregularly dilated lymphatics as well as lymphedema

However, the fundamental pathologic change is that of fibrotic thickening of the walls of the vessels in the deeper portions of the dermis, leading to occlusive changes in the lumina (Fig 59) Some of the vessels show thrombosis and recanalization The vessels nearest to the epidermis may show telangiectasia

Hair follicles and sebaceous glands are absent, but the sweat glands usually are preserved, except in areas of third degree injury The elastic tissue is, as a rule, less damaged than the collagenous tissue—at least in milder degrees of radiodermatitis In severe reactions, it is destroyed With Foot s reticulum stain, the reticulum fibers are seen to be increased throughout the dermis wherever there is formation of young connective tissue, but especially around blood vessels

In severe cases of chronic radiodermatitis, ulceration occurs The deep lying, large blood vessels beneath the ulcers, as a rule, show complete obliteration

The above described epidermal changes of dyskeratosis and intra epidermal carcinoma frequently lead on to invasive squamous cell carcinoma A fairly large percentage of them are of high (grade IV) malignancy and of the spindle celled variety (see page 338) In rare instances, basal cell epitheliomas develop in areas of radiodermatitis (Anderson and Anderson) (see under Basal Cell Epithelioma," page 370) The occurrence of sarcoma, on the other hand is not fully established Such instances have been reported (Blom Ides, Gentele), but always with the reservation that the diagnosis of spindle celled squamous-cell carcinoma could not be ruled out conclusively because this differentiation may be nearly impossible (see page 410) A point in favor of their being carcinoma is the fact that they are, in contrast to fibrosarcoma, radiosensitive (Blom Ides)

SOLAR DERMATITIS

Solar dermatitis may occur as erythematous, urticarial, papular or vesicular lesions in areas exposed to the sun The erythematous lesions may resemble lupus erythematosus in their clinical appearance by showing a livid red color and slight induration

but he concedes that differentiation of the two diseases by histologic means may be impossible Additional but not obligatory findings in the papular type of rosacea are superficial perifolliculitis with intrafollicular abscess formation (pustules) and dilatation of capil laries There is no hypertrophy of the sebaceous glands

In the glandular hyperplastic form the sebaceous glands are in creased in size and number The orifices of the sebaceous glands are dilated and filled with keratin and sebum There is an associated hypertrophy of the connective tissue The blood vessels are dilated A chronic inflammatory infiltrate is present around the vessels Peri folliculitis with intrafollicular abscess formation may be observed

FOX FORDYCE DISEASE

This disease occurs only in women It is characterized by an erup-

apocrine glands is the limitation of the eruption to the areas where apocrine glands occur and the onset of the disease at puberty when the apocrine glands begin to function Shelley and Hurley have ex pressed the opinion that Fox Fordyce disease may be basically a miliaria apocrina —in other words an apocrine sweat retention miliaria

Histopathology Histologic examination reveals acanthosis with hyperkeratosis The rete ridges are elongated A moderate degree of round cell infiltration is present around the blood vessels in the upper dermis The appearance thus is that of a chronic dermatitis

The apocrine glands appear normal (Roxburgh) The statement frequently found in the literature (Nilzén) that in Fox Fordyce dis ease the sweat glands are dilated is due to the fact that many authors have misinterpreted the apocrine glands as dilated sweat glands

ALOPECIA AREATA

Alopecia areata is characterized by loss of hair in one or

occasional instances the entire scalp is involved (alopecia totalis) in which case the loss of hair is usually permanent

Histopathology The hair follicles and the hair bulbs are greatly reduced in size The hair bulbs instead of being deep in the sub cutis are located quite high up in the dermis The hair follicles contain loose keratin and no hair In long standing cases there is

the infiltrate but there is no evidence of tuberculoid reaction At a later stage histiocytes and fibroblasts appear and fibrosis occurs

In lesions in which secondary bacterial infection is present one finds disintegration of the follicle and abscess formation Foreign body giant cells are then frequently found around the remnants of the follicle

ACNE VARIOLIFORMIS (ACNE NECROTICA MILIARIS)

Acne varioliformis is characterized by the presence of small indolent papules and pustules along the frontal hairline The lesions undergo central necrosis and tend to heal with pitted scars

Acne necrotica miliaris of the scalp is a diminutive variant of acne varioliformis Because of the superficial location of the necrosis no hair loss ensues

Histopathology The histologic changes of acne necrotica are similar to those of acne vulgaris except that the perifolliculitis is more limited in extent and almost invariably results in central necrosis Blood vessels adjacent to the necrotic area may be thrombosed Healing takes place with fibrosis and scar formation

Acne necrotica miliaris of the scalp shows the same histologic picture as that of acne varioliformis (Montgomery)

ACNE ROSACEA

Acne rosacea occurs in patients with seborrhea and affects the central portion of the face Two forms of rosacea exist the papular form and the glandular hyperplastic form The two forms may occur together The papular form is characterized by erythema papules pustules and telangiectases The glandular hyperplastic form causes enlargement of the nose called rhinophyma

Histopathology In the papular variety the infiltrate is either diffusely distributed throughout the dermis or arranged about the hair follicles and the sebaceous glands As a rule it is banal in character and composed largely of lymphocytes together with some histiocytes and plasma cells However a significant number of patients show in addition foci of epithelioid cells and Langhans giant cells occasionally lying in true tubercle formation so that the histologic picture is indistinguishable from that of cutaneous tuberculosis Miescher who found tuberculoid foci in 80 per cent of 59 patients with acne rosacea concluded that the rosacea like tuberculid of Lewandowsky and the papular type of acne rosacea represent the same disease (see page 183) On the other hand Laymon who observed tuberculoid structures in only 11 per cent of 138 patients with acne rosacea does not think that the two diseases are identical

Purpura occurs as the result of either noninflammatory or inflammatory changes in the walls of small blood vessels

Noninflammatory Purpura

The following types of purpura are noninflammatory stasis purpura due to increased intracapillary pressure senile purpura due to degeneration of the dermal collagen in exposed areas of the skin scurvy due to reduction of the intercellular material between endothelial cells thrombocytopenic purpura due to inadequate formation of blood platelets and febrile purpura with platelet thrombosis a rare systemic fatal disease

Histopathology In stasis purpura scurvy and thrombocytopenic purpura no visible vascular changes are present and the *only* abnormality consists of the presence of extravasated red blood cells and at a later stage of hemosiderin In senile purpura one observes in addition severe degenerative changes of the dermal collagen as seen in senile elastosis (see page 157) (Tattersall and Seville) In febrile purpura with platelet thrombosis one observes in the capillaries of the skin as well as of many internal organs degeneration and proliferation of endothelial cells and obstructing *thrombi composed* of platelets (Trobaugh)

Inflammatory Purpura (Vasculitis)

The following types of purpura are caused by inflammatory changes in the walls of small blood vessels (vasculitis) bacterial purpura due to meningococci *Streptococcus viridans* or other microorganisms anaphylactoid or Schoenlein Henoch purpura which is of unknown genesis and often associated with joint pains gastrointestinal bleeding and occasionally with glomerulonephritis purpura due to drug allergy and purpura associated with periarteritis nodosa

Histopathology There are vascular changes and an inflammatory infiltrate in addition to the extravasation of red blood cells

For the histologic changes in the purpuric lesions of meningococcemia and subacute bacterial endocarditis see pages 170 and 171 respectively For purpura associated with periarteritis nodosa see page 311 Purpura due to drug allergy has the same histologic picture as that of anaphylactoid purpura

Anaphylactoid Purpura Early lesions show prominent vascular changes in the upper dermis consisting of swelling and degeneration of endothelial cells and occasionally of focal necrosis of the vascular wall (Gairdner Levinson) A rather severe inflammatory infiltrate is

gross thinning of the dermis, which may be reduced to half its normal thickness (Dillaha and Rothman) In cases of recent onset, a mild to moderately severe inflammatory infiltrate composed of lymphocytes is seen in the deeper dermis about the vessels, the sebaceous glands and the hair follicles, while, in cases of more than 1 year's duration, the inflammatory reaction has subsided (Laymon) The sebaceous and the sweat glands appear normal throughout the course of the disease

ALOPECIA CICATRISATA (PSEUDOPELADE BROCQ)

In alopecia cicatrisata, *one finds scattered through the scalp irregularly shaped patches of alopecia which in the early stage may show perifollicular erythema but in the late stage show smooth atrophy* of the skin without any signs of inflammation The loss of hair is permanent

Histopathology. In the early stage, one finds a predominantly perifollicular infiltrate composed almost entirely of lymphocytes and a few histiocytes The infiltrate is present around the upper and the middle thirds of the follicles and spares the lower third It penetrates into the walls of the follicles and into the sebaceous glands, but not into the lumina of the follicles Follicular hyperkeratosis may be present (Miescher and Lenggenhager) Gradually, the infiltrate destroys the follicles and the sebaceous glands

In a late lesion, the epidermis is atrophic and the dermis shows fibrosis The follicles and the sebaceous glands are absent, but arrectores pilorum and sweat glands are, at least in part, preserved

Differential Diagnosis. In discoid lupus erythematosus, the inflammatory infiltrate not only is located around hairs and sebaceous glands but also is distributed in a patchy fashion throughout the dermis In addition, the epidermis shows liquefaction degeneration of the basal cell layer, hyperkeratosis and more marked keratotic plugging not limited to the follicles In the late cicatricial stage, a differentiation of the two diseases may be impossible

Folliculitis decalvans, which represents a folliculitis of the scalp, differs from alopecia cicatrisata by showing formation of intrafollicular *abscesses* (pustules) The perifollicular infiltrate often contains a fair number of plasma cells which are absent in alopecia cicatrisata (Miescher and Lenggenhager)

PURPURA

Purpura represents a hemorrhage into the skin Lesions less than 3 mm in diameter are called petechiae Larger lesions are called ecchymoses

non which occurs in sensitized animals at the site of a subcutaneous injection of foreign protein The presence of leukocytoclasis in anaphylactoid purpura would therefore support the view that this disease represents an allergic reaction (Ruiter and Brandsma)

PURPURA PIGMENTOSA PROGRESSIVA
(Majocchi Schamberg)

Four diseases are included under this term purpura annularis telangiectodes (Majocchi) progressive pigmentary dermatosis (Schamberg) pigmented purpuric lichenoid dermatitis (Gougerot and Blum) and angioma serpiginosum They are so closely related to one another that often they cannot be differentiated on clinical or histologic



Fig 61 Purpura pigmentosa progressiva (Majocchi Schamberg) A group of capillaries located in a papilla show swelling proliferation and degeneration of their endothelial cells A small focus of extravasation of erythrocytes can be seen to the right of the group of capillaries (×400)

present predominantly, but not exclusively, around the damaged vessels (Fig 60) It consists largely of neutrophils and varying amounts of eosinophils with only a few lymphocytes A characteristic feature is the presence of many scattered nuclear fragments the result of the disintegration of neutrophils (leukocytoclasis) Extravasation of



Fig 60 Anaphylactoid purpura (inflammatory purpura) The capillaries show swelling and degeneration of endothelial cells A rather severe inflammatory infiltrate is present especially around the capillaries It is composed largely of neutrophils many of which show disintegration of their nuclei (leukocytoclasis) This being an early lesion no extravasation of erythrocytes has as yet occurred (×200)

erythrocytes is usually present although it may be absent in the early stage of the disease

In older lesions extravasation of red cells usually is a prominent feature In addition hemosiderin may be present due to the decomposition of red cells The endothelial lining of the vessels may show proliferation The infiltrate contains fewer neutrophils and eosinophils and consists predominantly of lymphocytes However nuclear fragments are still present as a rule

It may be pointed out that fragmentation of the nuclei of neutrophils is prominent in the histologic picture of the Arthus phenome

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berg) pigmented purpuric lichenoid dermatitis (Gougerot and Blum) and angioma serpiginosum They are so closely related to one another that often they cannot be differentiated on clinical or histologic

grounds Their separation into different entities, therefore, is unwarranted (Randall, Kierland and Montgomery) The term purpura pigmentosa progressiva is suggested for this disease

The basic process is a chronic capillaritis of unknown cause occurring in the upper dermis and leading to capillary fragility Clinically, the primary lesion consists of purpuric puncta appearing in groups and slowly extending so that various sized patches form Gradually, pigmentation, due to the deposition of hemosiderin, supervenes and in cases of long standing, may dominate the clinical picture Inflammatory signs (such as erythema, scaling and papules) may be present or absent In most instances, the disease is limited to the lower extremities but may be more or less generalized The disease, though chronic, is harmless

Histopathology. In early lesions, the capillaries of the upper dermis show swelling degeneration and proliferation of their endothelial cells Often the number of capillaries appears to be increased Small amounts of extravasated red cells are usually found in the vicinity of some capillaries A cellular infiltrate, consisting largely of lymphocytes together with some histiocytes and occasionally a few neutrophils is present in the upper dermis, especially in the vicinity of the capillaries The inflammatory infiltrate may invade the lower epidermis and provoke mild liquefaction degeneration of the basal cell layer, mild spongiosis of the stratum malpighii and patchy parakeratosis

In older lesions, the number of capillaries is usually increased Some show proliferation of their endothelium and others dilatation of their lumen Extravasated red cells may no longer be present, but hemosiderin is almost always found, though in varying amounts The inflammatory infiltrate is less pronounced than in the early stage The epidermis may show slight atrophy with absence of the rete ridges

Differential Diagnosis It may be difficult to differentiate purpura pigmentosa progressiva histologically from stasis dermatitis because inflammation extravasation of erythrocytes and deposits of hemosiderin occur in both However the process extends much deeper in stasis dermatitis and in addition fibrosis of the dermis and fibrous thickening of the walls of medium sized vessels in the lower dermis is commonly present (see page 73) Anaphylactoid purpura differs from purpura pigmentosa progressiva by the predominance of neutrophils in the infiltrate and the presence of leukocytoclasis (see page 128)

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER CHRISTIAN DISEASE)

This disease is characterized by the appearance of crops of indurated, tender nodules and plaques in the subcutaneous fat. As the lesions involute, they often leave a depression in the skin. The over- [illegible] shows, as a rule, no involvement other than mild erythema [illegible]

Histopathology. Histologically, the disease can be [illegible] three stages. The first two stages occur while there is induration clinically. During the third stage, depression of the skin develops. The first stage is observed only rarely because it is of short duration. It is probable that it does not always occur. Most sections show a combination of the changes of the second and the third stage.

In the first stage (acute inflammatory stage), there is, between the fat cells, an inflammatory infiltrate composed of polymorphonuclear leukocytes, lymphocytes and histiocytes. Polymorphonuclear leuko-

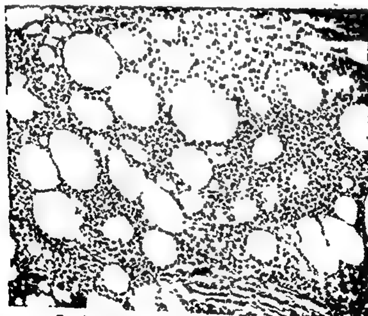


FIG. 62. Relapsing febrile nodular nonsuppurative panniculitis [illegible]

cytes may predominate (Fig 62) (Ungar Lever) Abscess formation does not occur

In the second stage (macrophagic stage) the infiltrate consists predominantly of histiocytes A few lymphocytes and plasma cells are present The histiocytes are seen invading and digesting the fat cells Such histiocytes (macrophages) are large and have a foamy cytoplasm

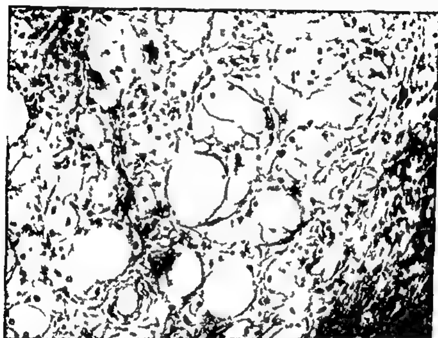


Fig 63 Relapsing febrile nodular nonsuppurative panniculitis Second and third stages The left side and the center of the field show the second stage foam cells (macrophages) invading and digesting the fat cells The right side shows the third stage re placement by fibrotic connective tissue (×100)

(Fig 63) Some of them are multinucleated In some areas numerous macrophages with foamy cytoplasm completely replace the fat cells

In the third stage (fibroblastic stage) fibroblasts intermingled with lymphocytes replace the macrophages Collagen is laid down with resulting fibrosis

The epidermis and the dermis show no involvement *In some cases* the subcutaneous vessels show pathologic changes such as edema and thickening of their walls (Cummins and Lever Tilden Gotshalk and Avakian)

In cases of liquefying panniculitis (Shaffer Binkley) the second macrophagic stage *instead of being followed by fibrosis* is followed

by liquefaction of the foam cell infiltrate One finds an amorphous foamy matrix in which the nuclei of foam cells as well as lymphocytes and some polymorphonuclear leukocytes are suspended

It is now established that the disease may affect the internal adipose tissue Four autopsies are on record In three of them internal lesions of panniculitis were present which had the same histologic appearance as the cutaneous lesions Involvement was slight in one of these cases (Spain and Foley) but extensive in two (Ungar Mostofi and Engleman) However only one of these patients (Mostofi and Engleman) had died definitely as a result of this disease

Differential Diagnosis The histologic appearance of nodular panniculitis is diagnostic in the second stage because there is no other condition in which one finds such preponderance of foam cells in the subcutaneous fat In foreign body granuloma one usually finds besides foam cells a great variety of other cells including foreign body giant cells

SCLEREMA NEONATORUM

Two types occur generalized sclerema neonatorum and nodular sclerema neonatorum (subcutaneous fat necrosis of the newborn adiponecrosis subcutanea neonatorum lipophagic granuloma)

In generalized sclerema neonatorum the skin of the entire body has a waxlike appearance and is hard dry and cold Death usually occurs within a week In nodular sclerema neonatorum one observes deep seated indurated areas in the subcutaneous fat The process is localized and self limited the lesions requiring about 4 months to disappear The general health is not affected

Histopathology The fundamental lesion is the same in generalized sclerema neonatorum and in nodular sclerema neonatorum (Zeek and Madden Flory) and both may occur simultaneously (Eichenlaub and Sandler) One finds degeneration necrosis and crystallization of the subcutaneous fat together with an inflammatory reaction and fibrosis It is possible that the disease is due to a delay in the maturation of the fat and that on account of this there is an unusually low oleic acid content of the fat so that it solidifies more easily than normally (Noojin Pace and Davis)

Generalized Sclerema Neonatorum The fat cells of the subcutis vary greatly in size and shape In some areas they are necrotic and have lost their outline Needle-shaped empty clefts lie singly or in radial arrangement inside of fat cells (Fig 64) In frozen sections these clefts are found to be occupied by crystals The crystals fail to stain with fat stains Some of them are doubly refractile in the polarizing microscope (Reich Zeek and Madden) The chemical composi

tion of the crystals is not yet established fully. Most investigators regard the crystals as those of fatty acids (McIntosh). A granulomatous infiltrate is present mainly at the periphery of the fat lobules but also in scattered foci throughout the lobules. The infiltrate is composed of lymphocytes, histiocytes, foreign-body giant cells and fibroblasts. The septa between the fat lobules are considerably thickened.

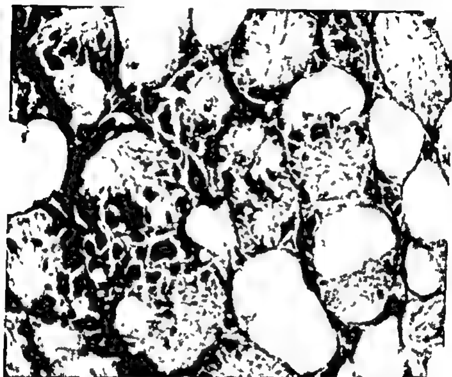


FIG 64 Sclerema neonatorum (subcutaneous fat necrosis of the newborn). Several fat cells contain needle shaped clefts in a radial arrangement. These clefts are indicative of fat crystals. The fat crystals themselves are not visible because of fixation in Helly's solution, which dissolves fat. A granulomatous infiltrate containing foreign body giant cells is present between the fat cells (×100)

In two cases of generalized sclerema neonatorum, autopsy revealed in the visceral fat lesions which were histologically identical with those of the subcutaneous fat. In one case (Zeek and Madden), the lesions were widely distributed. In the other case (Flory), they were limited to the perirenal fat and to the fat about the ribs.

NODULAR SCLEREMA NEONATORUM (SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN). One observes, as a rule, a more marked inflammatory reaction and a much larger number of foreign body giant cells than in generalized sclerema neonatorum (Fig 64). The foreign-

body giant cells may contain fat crystals (Fox) Healing takes place with fibrosis

Differential Diagnosis The histologic picture of sclerema neonatorum differs from that of relapsing febrile nodular nonsuppurative panniculitis by the presence of fat crystals and the absence of foam cells

HEREDITARY EDEMA OF THE LEGS (MILROY S DISEASE)

This disease occurs as a solid white indolent and persistent edema of the lower extremities Usually several members of a family are affected

Histopathology The dermis and especially the subcutaneous fat show severe interstitial edema There is an increase in the amount of collagen in the dermis and segmentation of the subcutaneous fat by thick strands of collagen The capillaries and the lymphatics are dilated and increased in number and show slight perivascular lymphocytic infiltration The walls of the larger blood vessels may be thickened by fibrosis

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

In this disorder one or several small well-defined hard painful nodules are found on the upper margin of the ear The surface of the nodules often is hyperkeratotic After removal of the keratotic layer a small ulcer may be visualized

Histopathology The epidermis shows hyperkeratosis irregular acanthosis and usually also central ulceration The dermis and frequently also the perichondrium are permeated by a chronic inflammatory granulomatous infiltrate composed of lymphocytes plasma cells [illegible]

and severity There n [illegible]
cells but occasionally [illegible] generation so that the cartilage instead of staining blue stains homogeneously pink with hematoxylin and eosin in the affected areas

The pathogenesis is not clear Whereas most authors regard degenerative changes in the cartilage as the primary change (Foerster Fhenius) Newcomer recently has pointed out that similar degenerative changes occur in the aural cartilage with advancing age It is probable that trauma such as frostbite or pressure causes focal degeneration in the dermis of the ear Due to poor vascularization

in the affected area, repair does not ensue and the lesion becomes a focus of chronic inflammation.

SCABIES

Scabies, which is caused by the itch mite, *Acarus scabiei*, presents burrows as its characteristic lesion. The burrows, produced by the female mite, occur on the palmar surfaces of the hands and the fingers,



Fig 65 Scabies (Norwegian scabies) Two female mites are located entirely within the horny layer of the epidermis (×200) (Robert N Buchanan, Jr, M D)

on the interdigital skin, on the flexor surfaces of the wrists, on the nipples of women and on the genitals of men They appear as fine, angular or tortuous blackish threads, a few millimeters long Often a vesicle is visible near the blind end of the burrow In addition to the burrows, scabies presents a papular eruption which is usually most pronounced on the abdomen, the lower portions of the buttocks and the anterior axillary folds

In especially susceptible individuals, the clinical picture of so called Norwegian scabies may result, showing diffuse hyperkeratosis, scaling and crusting of the skin and burrows everywhere on the skin, even on the face and the scalp

Histopathology Histologic examination reveals the burrow in almost the whole of its course limited to the horny layer Only the extreme blind end of the burrow is either in contact with or extends into the stratum malpighii The female mite is situated at the blind end of the burrow (Fig 65) Its head is bored more or less deeply into the stratum malpighii Intracellular and intercellular edema is present in the stratum malpighii beneath the mouth parts of the mite to such extent that vesicle formation often results The mite thus takes its food in fluid form The dermis beneath the burrow shows a chronic inflammatory infiltrate which is composed predominantly of lymphocytes

Norwegian scabies shows a much greater number of burrows than ordinary scabies so that almost every section shows several of them (Ingram)

INSECT BITES

Insect bites especially when caused by ticks may cause persistent lesions which pose a diagnostic problem clinically as well as histologically The clinical appearance of the lesions usually is that of a firm papule or of a nodule with or without central ulceration

Histopathology The epidermis frequently shows pseudo epitheliomatous hyperplasia (see page 331) The dermis presents a dense granulomatous infiltrate which often extends into the subcutaneous fat It consists principally of eosinophils and plasma cells admixed with lymphocytes and histiocytes Some of the histiocytes occasionally show nuclei that are hyperchromatic show mitotic figures or are binucleated In some lesions large lymphoid follicles with germinal centers are observed (Winer and Strakosch Allen) In rare instances parts of the insect are found in the dermis either free in the tissue surrounded by a foreign body reaction or within an epidermal inclusion cyst (Allen)

Differential Diagnosis If parts of the insect are present in the section the diagnosis is obvious In their absence the true nature of the lesion may be missed easily The pseudo epitheliomatous hyperplasia must be differentiated from squamous-cell carcinoma (see page 329) The presence of mitotic figures in the histiocytes together with the large number of eosinophils may suggest mycosis fungoides the presence of lymphoid follicles may suggest lymphocytoma cutis and the binucleated histiocytes if present require differentiation from the Sternberg Reed cells of Hodgkin s disease However the abundance of plasma cells in association with the eosinophils usually rules out lymphoma

LICHEN URTICATUS (PAPULAR URTICARIA)

This is a recurrent, pruritic eruption occurring, especially in children, during the summer months. The lesions consist of edematous

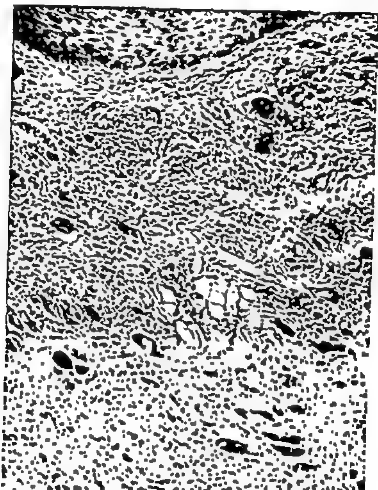


FIG. 66 Foreign body granuloma caused by a silk suture The silk suture is located in the center of the field Around it there is a severe inflammatory infiltrate containing numerous foreign body giant cells (×200)

papules Sensitivity to flea and bedbug bites is now generally regarded as the usual cause (Goldman; Shaffer, Spencer and Blank).

Histopathology. The appearance is nonspecific Acanthosis and, in some cases, hyperkeratosis are present The stratum malpighii shows intercellular as well as intracellular edema A rather pronounced chronic inflammatory infiltrate is present around the vessels of the upper dermis.

FOREIGN BODY GRANULOMAS

Many foreign substances when injected or accidentally implanted into the skin may cause a foreign body reaction In addition certain



Fig 67 Lipid granuloma caused by mineral oil (paraffinoma) The many large and small ovoid or round cavities which give the section a Swiss cheese appearance represent spaces filled with mineral oil (paraffin) (×200)

substances formed within the body may produce a foreign body reaction when deposited in the dermis or in the subcutaneous tissue Examples are the

epithelioma o

cysts

Histopathology A typical foreign body reaction shows around the foreign material histiocytes and foreign body giant cells (for

their description, see page 36) In addition, lymphocytes and plasma cells are present (Fig 66) The histiocytes and the giant cells often exhibit phagocytic activity and then contain some of the foreign material

Some foreign body granulomas have a rather specific appearance Among them are lipid, tattoo, silicon and beryllium granulomas

Lipid Granuloma (Paraffinoma)

Granulomas following injections of oily substances such as mineral oil (paraffin), cotton oil, or camphor oil occur as irregular, hard, nodular subcutaneous swellings Ulceration may develop

Histopathology. Histologically, lipid granulomas have a Swiss cheese' appearance because of the presence of numerous ovoid or round cavities (Fig 67) These cavities represent spaces occupied by the oily substance (Conrad and Weiss) The spaces between the cavities are taken up by an infiltrate composed largely of lymphocytes and some plasma cells In addition, there are groups of histiocytes some of which, due to the ingestion of lipid, have a foamy cytoplasm Variable numbers of foreign body giant cells are present In older lesions fibrosis is prominent

Under the term sclerosing lipogranuloma, Smetana and Bernhard have reported as a post traumatic process subcutaneous granulomas with the same histologic picture as just described However, Best Mason, DeWeerd and Dahlin have thrown serious doubt on the existence of such an entity Investigating two similar cases, they found by chemical analysis that the lipid' material was not body fat but mineral oil The lipid material in their cases stained with Sudan 4 *but not with osmic acid*

Tattoo Granuloma

Histopathology. Ordinary tattoos show diffusely scattered granules in the upper half of the dermis within phagocytes and lying free in the tissue, without any inflammatory reaction

However, if an inflammatory reaction occurs, due to allergy, the inflammatory infiltrate shows aside from the phagocytes numerous lymphocytes with an admixture of many eosinophils and a few plasma cells (Rostenberg Brown and Caro)

Silicon Granuloma

Silicon may be introduced into the skin through the contamination of lacerations with particles of soil Such wounds heal at first and then, many months or years later indurated nodules develop in the skin or the subcutaneous tissue

Histopathology. The histologic picture is indistinguishable from that of sarcoidosis (see page 188) except for the presence in some of the giant cells of colorless, spiculated, crystalline particles varying in [illegible] barely visible to 100 microns in length. When examined [illegible]

Beryllium Granuloma

Beryllium granulomas of the skin may form in two different ways (Grier, Nash and Freiman). They may arise as a manifestation of



Fig. 69. *Beryllium granuloma caused by laceration with a fluorescent light tube.* There is a large *area of* caseation necrosis surrounded by tuberculoid granulation tissue. *To the left* several sarcoid-like epithelioid-cell islands are present. (×100)

systemic berylliosis, in which case it must be assumed that particles of beryllium reached the skin through the circulation, or they may develop following a laceration of the skin through which beryllium entered the tissue. Such lacerations were observed some years ago from cuts with fluorescent light bulb[illegible]

their description, see page 36) In addition, lymphocytes and plasma cells are present (Fig 66) The histiocytes and the giant cells often exhibit *phagocytic activity* and then contain some of the foreign material

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nodules over which the skin remains intact They are always few in number The most serious lesion in systemic berylliosis is the chronic progressive pneumonitis which is frequently fatal

The cutaneous granulomas following laceration show as first sign incomplete healing of the laceration, followed by swelling, induration and tenderness and, finally, central ulceration

Histopathology. *The cutaneous granulomas of systemic berylliosis* often are indistinguishable from sarcoidosis (Hardy and Tabershaw) Occasionally, however, *a moderate amount of caseation necrosis is* present in some of the epithelioid cell islands The quantity of beryllium *present in the lesions is too small to be demonstrable* by spectrographic analysis

The cutaneous granulomas following laceration show, as a rule, more caseation necrosis than the granulomas of systemic berylliosis The *caseation necrosis not only may be present within* some of the epithelioid cell islands but also may affect the entire center of the *lesion* (Fig 68) (Neave, Frank and Tolmach) *A collar of lymphocytes* often surrounds some of the epithelioid cell islands, giving them the appearance of true tubercles *Occasionally, Schaumann bodies,* just like those of sarcoidosis, are present (Grier, Nash and Freiman) The epidermis shows acanthosis and may show ulceration *In some cases* the presence of beryllium has been demonstrated by spectrographic analysis (Dutra)

SWIMMING POOL GRANULOMA

Abrasions in swimming pools may lead to circumscribed areas of nodular infiltration on the face resembling lupus vulgaris (Hellerstrom) or to granulomatous, verrucous lesions on the knee or elsewhere resembling tuberculosis verrucosa cutis (Rees and Bennett) The lesions usually heal within 3 to 9 months

Histopathology. *The histologic picture is similar to that of lupus vulgaris* (Hellerstrom) or of tuberculosis verrucosa cutis (Rees and Bennett) Hellerstrom regarded his cases as instances of *inoculation* lupus vulgaris but inoculations of tissue into guinea pigs have given negative results in all reported cases and Hellerstrom found acid fast bacilli in the tissue in but one of his six cases Thus a tuberculous cause is not established Silicon granuloma is also unlikely because no crystalline particles were ever observed The cause remains obscure

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9

Eruptions Due to Drugs

Allergic reactions to drugs may cause various *eruptions identical in* their clinical appearances to cutaneous diseases occurring also as idio pathic entities Drugs may cause, for instance, urticaria, erythema *multiforme*, erythema nodosum, dermatitis, including generalized exfoliative dermatitis, purpura, folliculitis and *periarteritis nodosa* The histologic picture is the same in these diseases whether they are due to a drug or occur in their idiopathic form

Only histologic changes more or less specific for eruptions due to drugs will be discussed

FIXED DRUG ERUPTION

Fixed drug *eruptions are circumscribed* lesions which persistently recur at the same site at each administration of the allergenic drug The most common type of fixed drug eruption consists of one or several slightly elevated, erythematous plaques which on healing leave pigmented areas Fixed drug eruptions may occur after the ingestion of phenolphthalein and coal tar derivatives such as amino pyrine and acetophenetidin

Histopathology. *There is an increase in melanin in the basal* cells and in the dendritic cells of the epidermis Melanin is present in the upper dermis It is found predominantly in histiocytes (melano phores) but also free in the tissue The superficial capillaries are sur rounded by a mild inflammatory infiltrate composed of lymphocytes and histiocytes (Weiss and Kile Chargin and Leifer)

QUINACRINE HYDROCHLORIDE (ATABRINE) DERMATITIS

Quinacrine hydrochloride (Atabrine) may cause a subacute or a chronic dermatitis, lichen planus like lesions and exfoliative derma titis (Bereston) *In some patients the eruption* is followed by anhi drosis in the involved areas

Histopathology The histologic picture is usually that of a non specific chronic dermatitis In lesions that clinically resemble lichen planus, the histopathologic picture often resembles that of lichen

planus too As a rule however, the bandlike infiltrate is not so dense as in lichen planus and may contain eosinophils which are not present in true lichen planus (Wilson) In many cases one observes hyperkeratosis with keratotic plugging of pilosebaceous follicles Numerous melanophores may be present in the dermis (Alden and Frank)

In patients in whom anhidrosis develops in areas of quinacrine hydrochloride dermatitis one may observe atrophy of the dermal portions of sweat ducts and dilatation and atrophy of the sweat glands Focal inflammation may be present about the sweat glands (Sulzberger Herrmann and Zak)

EXFOLIATIVE DERMATITIS DUE TO DRUGS

The most common drugs to cause exfoliative dermatitis are arsphenamine gold salts the sulfonamides and phenobarbital

Histopathology The exfoliative dermatitis caused by these drugs has the same histologic appearance as exfoliative dermatitis due to other causes (see page 74 and Fig 27)

Changes in the internal organs may be present such as interstitial myocarditis (Brown and McNamara French and Weller Winer and Baer) interstitial nephritis (Winer and Baer) and fatty degeneration of the liver with inflammatory infiltration about the portal canals (Winer and Baer)

BROMODERMA

Prolonged ingestion of bromides may cause the formation of granulomatous verrucous plaques which are called bromoderma They occur usually on the lower extremities

Histopathology There are papillomatosis and considerable downward proliferation of the epidermis often of such degree as to produce the picture of pseudo epitheliomatous hyperpla[illegible]

[illegible] dermis (Bloch and Fenchio) (Fig 69) The dermis shows an extensive granulomatous infiltrate which may reach down into the subcutaneous layer It is composed of a great variety of cells including lymphocytes plasma cells and histiocytes Neutrophils are usually numerous and abscesses may be found scattered through the infiltrate Eosinophils are few or absent The blood vessels are increased in number are dilated and show proliferation of their endothelium Small areas of hemorrhage are often seen within the infiltrate

Differential Diagnosis The histologic picture of bromoderma is suggestive but not diagnostic Pyoderma gangrenosum may show at

the margin of an ulcer, an identical histologic picture, including intra epidermal abscesses Intra epidermal abscesses are also observed in older lesions of pemphigus vegetans and in blastomycosis Pemphigus vegetans differs from bromoderma by the large percentage of eosinophils in the intra epidermal abscesses and in the granuloma

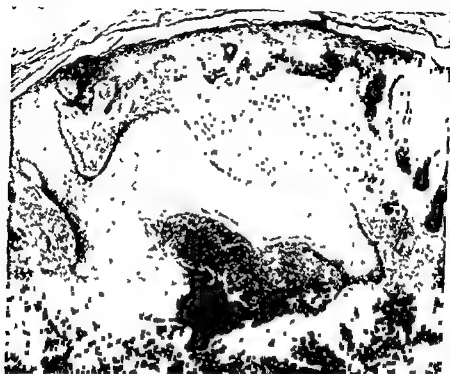


Fig 69 Bromoderma There is downward proliferation of the epidermis A large intra epidermal abscess is shown The dermis contains a granulomatous infiltrate (×50)

tous infiltrate (see page 80) Blastomycosis is easily differentiated by its numerous giant cells and the presence of yeast cells in them

IODODERMA

Iododerma is characterized by granulomatous lesions which may have the same clinical appearance as bromoderma As a rule, however, there is less verrucous proliferation and greater tendency to ulceration

Histopathology. Histologically iododerma differs from bromoderma by showing less epithelial proliferation The granulomatous infiltrate frequently destroys the epidermis resulting in ulceration The infiltrate may be composed predominantly of histiocytes some of which may show mitotic figures and hyperchromatic nuclei, so that

distinction from lesions of mycosis fungoides in the tumor stage may be almost impossible (Eller and Fox, Hollander and Fetterman).

ARGYRIA

This condition, caused by prolonged ingestion of silver salts or their local application to the mucous membranes, is characterized by



Fig. 70. Argyria. Silver granules are present in the membrana propria of the sweat glands. In some places the granules are so dense that they form a solid black band. (×100)

bluish gray slate colored discoloration of the entire skin, most pronounced on the exposed portions of the skin.

Histopathology. Silver is found in the dermis, predominantly extracellularly, as fine, small, round, brownish particles of uniform size. It is never seen in the epidermis or its appendages. The silver particles measure less than 1 micron in diameter and lie singly as well as in clumps. Although visible in routine stains, they appear more clearly in sections stained lightly with polychrome methylene blue. However, the best method for the demonstration of silver granules is by dark field illumination. If sections are placed under a dark field microscope, the silver appears as brilliantly refractile, white granules

against a dark background Many more granules can be seen than with direct illumination

The silver granules are most numerous in the membrane propria surrounding the sweat glands (Fig 70) and in the subepidermal dermis *In addition silver particles may be seen in the connective* tissue sheaths about the hair follicles and the sebaceous glands in the walls of blood vessels particularly their intima and adventitia in the arrectores pilorum and the nerves and diffusely scattered through the middle and the lower dermis Elastic tissue stains reveals *a predilection of the granules of silver for elastic fibers* The location of silver in elastic fibers explains the presence of fingerlike chains of granules projecting into the papillary bodies (Hill and Montgomery) In many cases one finds increased amounts of melanin in the basal layer of the epidermis and melanin laden chromatophores in the dermis

Silver is deposited not only in the skin but also in internal organs It is found particularly in the intima of blood vessels and in the connective tissue of the internal organs Analogous to the marked involvement of the basement membrane of the sweat glands the basement membranes around the acini of the testes and of the choroid plexus are particularly rich in granules (Harker and Hunter)

Differential Diagnosis *Histologic differentiation of* argyria *from* other kinds of pigmentation is made readily Melanin and hemosiderin possess larger granules which lie to a great extent intracellularly in chromatophores and are nonrefractile with dark field illumination In pigmentation due to mercury whether from the use of *creams or in tattoo marks the mercury is deposited in large coarse* granules throughout the epidermis and the dermis without any special affinity for the membrana propria of the sweat glands For differentiation from chrysiasis see below

CHRYSIASIS

In chrysiasis which may follow the parenteral use of gold salts the skin of the exposed parts shows an ash gray discoloration

Histopathology Gold granules are light refractile with dark field examination like silver granules but they are larger and more irregular in size than silver granules *In contrast to silver granules they* are found predominantly within cells They lie in the endothelial and the perithelial cells of capillaries and in macrophages throughout the upper dermis Only occasionally do granules lie free in the tissue spaces (Schmidt) In some instances gold particles are found in the basal cells of the epidermis (Kochs)

ARSENICAL KERATOSIS AND CARCINOMA

Prolonged ingestion of inorganic arsenic frequently produces multiple arsenical keratoses which may progress into squamous-cell carcinoma. Recently it has been suggested that not only multiple cutaneous cancers but also multiple internal cancers may be caused (Sommers and McManus). Occasionally multiple superficial basal cell epitheliomas form in addition to arsenical keratoses (Anderson; Montgomery and Waisman).

Arsenical keratoses resemble senile keratoses in their clinical appearance. They may occur anywhere on the skin but are found most frequently on the palms and the soles, in contrast with senile keratoses which predominate on the face and on the dorsa of the hands.

Histopathology. In early arsenical keratoses one observes hyperkeratosis associated with acanthosis and irregular downward proliferation of the rete ridges. There usually is some degree of disorder of the squamous cells and pyknosis of some of the nuclei. The histologic picture thus resembles that of senile keratosis (see page 327).

In more advanced lesions, in addition to the above-mentioned fe... res ...

... pronounced than in Bowen's disease. Although vacuolization of cells occurs also in Bowen's disease, this feature is not so prominent as in arsenical keratosis. The presence of numerous vacuolated cells may be regarded as diagnostic of arsenical keratosis (Montgomery and Waisman). The vacuolated cells are twice or three times as large as normal squamous cells and possess small, irregular, deeply staining nuclei. They resemble the Paget cells of Paget's disease of the nipple except that intercellular prickles are usually present.

Ultimately, through invasion of the dermis, frank squamous-cell carcinoma may develop (see page 329). Even in the invading type of carcinoma, vacuolization, clumping and dyskeratosis remain prominent.

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10

Degenerative Diseases

SENILE DEGENERATION

Senile changes in skin not regularly exposed to light manifest themselves clinically in thinning of the skin and atrophy of the subcutaneous fat. In exposed skin the changes usually are much more pronounced than in skin that is not exposed and include marked

skin after minor trauma ecchymoses may occur (senile purpura)

In xposed to light senile rete ridges and atrophy changes in the collagen or in the elastic tissue are absent. Mild obliterative changes may be found in some of the vessels (Hill and Montgomery).

In skin exposed to sunlight two types of degenerative changes are seen which however represent one and the same process: basophilic degeneration of the collagen and senile elastosis. These changes limited to the upper third of the dermis may start as early as in the third decade of life and progress with age.

In basophilic degeneration the collagenous fibers appear broken up into amorphous clumps and granules which stain faintly

are stained with orcein as for elastic tissue. One then observes in the upper dermis separated from a somewhat atrophic epidermis by a narrow band of normal collagen masses of twisted thick black-staining fibers (Fig. 71). Because these fibers give the same staining reactions as elastic tissue Unna referred to them as collastin thinking they were the result of a merging of collagen with elastic fibers. However recent studies by x-ray diffraction and electron microscopy suggest that the essential change in senile elastosis is degeneration of collagen fibers. Furthermore the degenerated material can be removed—in contrast with elastic fibers—by treatment of the sections with trypsin and at the same time the

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xerotica obliterans formerly regarded as independent diseases probably are identical with lichen sclerosus et atrophicus (see below)

Histopathology In lichen sclerosus et atrophicus one observes (1) hyperkeratosis with keratotic plugging (2) atrophy of the stratum



FIG 72 Lichen sclerosus et atrophicus There are hyperkeratosis with follicular plugging, atrophy of the stratum malpighii marked lymphedema of the upper dermis and an inflammatory infiltrate in the mid dermis The edema in the subepidermal dermis is so marked that a bulla has resulted. (×100)

...ue in the mid-dermis (Fig 72)

The hyperkeratosis is so marked that often the horny layer is thicker than the atrophic stratum malpighii The stratum malpighii is reduced to a few layers of flattened cells The cells of the basal layer show hydropic degeneration The rete ridges often are completely

elastic staining properties of the skin disappear (Tattersall and Seville) This suggests that the increase in orcein staining material is caused not by an increase in the amount of elastic tissue but by a false staining reaction of degenerated collagen Staining of frozen sections with fat stains occasionally reveals numerous fine lipid droplets in the areas of basophilic degeneration or senile elastosis (Weidman Percival Hannay and Duthie)



FIG 71 Senile degeneration (senile elastosis) In the upper derm is separated from the epidermis by a narrow band of normal collagen there are masses of twisted thick degenerated collagen fibers staining black with orcein—just like elastic tissue (×100)

Differential Diagnosis For differentiation from pseudoxanthoma elasticum see page 56

LICHEN SCLEROSUS ET ATROPHICUS

This disorder is characterized by flat topped white papules which coalesce to form white patches without any infiltration The surface of the lesions often shows comedo like plugs Occasionally the patches become bullous due to accumulation of fluid beneath the epidermis Lichen sclerosus et atrophicus occurs not only on the skin but also on the vulva and the glans penis Kraurosis vulvae and balanitis

wiped out but they may persist in some areas and even show some irregular downward proliferation. In such proliferations, hydropic degeneration of the basal cells usually is pronounced.

Beneath the epidermis there is a broad zone of pronounced edema. Within this zone the collagenous fibers are swollen and homogeneous and contain only a few nuclei. They stain poorly with eosin and other connective tissue stains. This change does not represent sclerosis (as the name of the disease would imply) but lymphedema. The hydropic degeneration of the basal cells together with the edema of the subepidermal collagen may lead to the formation of subepidermal bullae (Gottschalk and Cooper). These bullae may thus be classified as being due to degeneration of the basal cells (see "Classification of Bullae," page 66). The elastic fibers are sparse or even absent in the zone of edema (Nomland).

In the mid-dermis, beneath the area of edema, there is an infiltrate which usually is perivascular but at times assumes a bandlike formation. It is composed almost exclusively of lymphocytes. In lesions of long duration the infiltrate may have almost disappeared.

KRAUROSIS VULVAE

A satisfactory classification of the atrophic lesions of the vulva has not yet evolved and, to a certain degree, the vagueness of the term kraurosis vulvae is responsible for this. Although some authors still regard it as an entity (Wallace and Whimster), others regard it as *synonymous* with lichen sclerosus et atrophicus (Laymon).

The simplest classification of the atrophic lesions of the vulva that can be offered at present is:

1. SENILE OR PRESENILE ATROPHY. There is atrophy of the vulvar *mucosa* but no stenosis of the vaginal orifice. There may be itching, and, due to scratching, a vulvitis may result.

2. LICHEN SCLEROSUS ET ATROPHICUS ("KRAUROSIS VULVAE"). Considerable atrophy with stenosis of the vaginal orifice is present. The lesions are whitish in color, sharply demarcated and may extend to the inguinal folds and the perianal region. Itching may be present. Because the lesions have a whitish color, on casual inspection they resemble leukoplakia, but they lack the induration observed in leukoplakia. There has been uncertainty as to whether lichen sclerosus et

FIG. 75. Kraurosis vulvae (lichen sclerosus et atrophicus). There are edema of the upper dermis and a bandlike inflammatory infiltrate beneath it. In addition, there is irregular downward proliferation of the rete ridges with hydropic degeneration of the basal cells. The latter feature is typical of lichen sclerosus et atrophicus and rules out leukoplakia. (×100)



FIG 73 Kraurosis vulvae (lichen sclerosus et atrophicus). There are hyperkeratosis atrophy of the stratum malpighii and marked lymph edema of the upper dermis with homogenization of the collagen (×100)

FIG 74. See facing page for legend.

wiped out but they may persist in some areas and even show some irregular downward proliferation. In such proliferations, hydropic degeneration of the basal cells usually is pronounced.

Beneath the epidermis there is a broad zone of pronounced edema. Within this zone the collagenous fibers are swollen and homogeneous and contain only a few nuclei. They stain poorly with eosin and other connective tissue stains. This change does not represent sclerosis (as the name of the disease would imply) but lymphedema. The hydropic degeneration of the basal cells together with the edema of the subepidermal collagen may lead to the formation of subepidermal bullae (Gottschalk and Cooper). These bullae may thus be classified as being due to degeneration of the basal cells (see "Classification of Bullae," page 66). The elastic fibers are sparse or even absent in the zone of edema (Nomland).

In the mid dermis beneath the area of edema there is an infiltrate which usually is perivascular but at times assumes a bandlike formation. It is composed almost exclusively of lymphocytes. In lesions of long duration the infiltrate may have almost disappeared.

KRAUROSIS VULVAE

A satisfactory classification of the atrophic lesions of the vulva has not yet evolved and, to a certain degree, the vagueness of the term kraurosis vulvae is responsible for this. Although some authors still regard it as an entity (Wallace and Whimster), others regard it as synonymous with lichen sclerosus et atrophicus (Laymon).

The simplest classification of the atrophic lesions of the vulva that can be offered at present is:

1. Senile or Presenile Atrophy. There is atrophy of the vulvar mucosa but no stenosis of the vaginal orifice. There may be itching and, due to *scratching*, a vulvitis may result.

2. Lichen Sclerosus et Atrophicus ("Kraurosis Vulvae"). Considerable atrophy with stenosis of the vaginal orifice is present. The lesions are whitish *in color*, sharply demarcated and may extend to the *inguinal* folds and the perianal *region*. Itching may be present. Because the lesions have a whitish color, on casual inspection the resemble le... l...

plakia. T

Fig. 74. Kraurosis vulvae (lichen sclerosus et atrophicus). There are edema of the upper dermis and a bandlike inflammatory infiltrate beneath it. In addition, there is irregular downward proliferation of the rete ridges with hydropic degeneration of the basal cells. The latter feature is typical of lichen sclerosus et atrophicus and rules out leukoplakia. (×100)

atrophicus, a perfectly harmless lesion elsewhere, may progress into leukoplakia and squamous cell carcinoma when occurring on the vulva. Such instances recently have been reported (Wallace and Whimster), but it seems to be rare. Nevertheless, as Wallace and Whimster state, any state of atrophy occurring on the vulva has malignant potentialities.

3. Leukoplakia. One or several whitish indurated plaques are present. Leukoplakia may occur independently or secondary to senile atrophy of the vulva. Since leukoplakia is an early malignant lesion ("squamous cell carcinoma, grade ½," see page 328), development of squamous cell carcinoma is common.

Histopathology. The histologic picture of senile or presenile atrophy is nonspecific, consisting of atrophy of the epidermis and a mild to moderately severe chronic inflammatory infiltrate in the upper dermis.

Lichen sclerosus et atrophicus of the vulva (kraurosis vulvae) shows the same histologic picture as on the skin with the exception that lesions located on the mucous membranes show no keratotic plugs (Fig. 73). Irregular downward proliferation of the rete ridges in which the basal cells show considerable hydropic degeneration occur more often than on the skin (Fig. 71). They should not be confused with the early atypical proliferations of leukoplakia which do not contain such hydropic basal cells.

Leukoplakia shows atypicality of the epidermis with irregular downward proliferation of atypical cells (see page 328). The hydropic degeneration of the basal cells seen in lichen sclerosus et atrophicus is absent.

BALANITIS XEROTICA OBLITERANS

Balanitis xerotica obliterans represents lichen sclerosus et atrophicus of the glans and prepuce (Laymon). It is a chronic, progressive atrophic process which frequently eventuates in urethral stenosis. In very rare instances, carcinoma may supervene (Grutz).

Histopathology. The histologic picture is that of lichen sclerosus et atrophicus. Because of the absence of follicles in the areas of involvement, no keratotic plugging occurs.

STRIAE DISTENSAE

Striae distensae occur in pregnancy and obesity, and particularly in Cushing's disease. They represent linear areas of cutaneous atrophy.

Histopathology. In the early lesions, the elastic fibers are transformed into numerous faintly staining fibrillae due to fraying of the elastic fibers. In addition, there are a mild perivascular infiltrate and

a distortion of the collagen bundles Old lesions show almost complete absence of elastic fibers in the center At the margin coiled and clumped elastic fibers are interspersed with fine, poorly staining fibrillae

On the basis of these findings Ebert has concluded that striae distensae are not due to mechanical tearing of elastic fibers alone but that degeneration of the elastic fibers precedes their disappearance in the center of the striae

MACULAR ATROPHY (ANETODERMA)

Macular atrophy of Schweninger and Buzzi or anetoderma is characterized by atrophic oval patches located particularly on the trunk The skin of the patches is thin and bluish white and bulges slightly The lesions may give to the palpating finger the same sensation as does a hernial orifice Early lesions may show mild erythema

In the literature a difference has been made between a primary idiopathic type of macular atrophy and a secondary type developing in patients with diseases such as syphilis lupus erythematosus and acrodermatitis chronica atrophicans but in sites not clinically affected by these diseases (Scull and Nomland) It is likely that such association is merely coincidence

[illegible]

pe [illegible]
les [illegible] disappearance of the elastic tissue throughout the dermis The collagen remains unaffected Thus a diagnosis of this disease can be made only from sections stained for elastic tissue

ATROPHODERMA RETICULATUM (FOLLICULITIS ULERYTHEMATOSA RETICULATA)

The eruption which is limited to the sides of the face consists of numerous small closely set areas of atrophy separated by narrow ridges of normal skin resulting in a reticulated appearance

Histopathology The epidermis shows diminution of the number of rete ridges and follicular plugging Horn cysts caused by keratinization of hair follicles are present in the dermis Sebaceous glands are few in number and small in size In addition one observes degeneration of the collagen and fragmentation of the elastic fibers

COLLOID MILIUM (COLLOID DEGENERATION OF THE SKIN)

Colloid milium is characterized by pinhead sized round sharply circumscribed yellowish nodules of the skin The nodules have a

translucent appearance and on puncture give exit to a soft gelatinous mass The forehead is the site of predilection

In occasional instances instead of small nodules large plaquelike lesions are present To such cases the term colloid degeneration of the skin has been applied (Reuter and Becker)

Histopathology Histologically colloid milium is characterized by the presence of circumscribed masses of colloid material in the subepidermal region It is assumed by many that colloid represents a form of collagen degeneration Pinkken has observed that collagen before becoming colloid passes through the stage of basophilic degeneration However it is possible that colloid like amyloid represents a deposit rather than a product of collagen degeneration (Percival and Duthie)

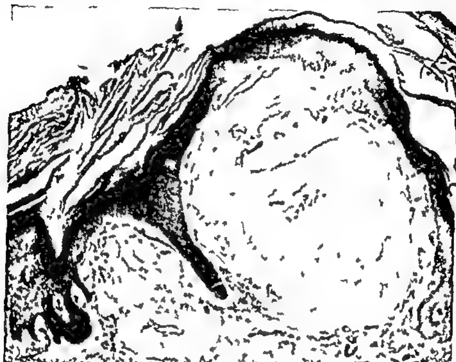


Fig 75 Colloid milium In the upper dermis separated from the epidermis by a narrow zone of normal collagen there are two large *round spaces incompletely filled with fissured mass of homogeneous* material This material represents colloid The colloid contains a moderate number of nuclei (×100)

The epidermis shows hyperkeratosis and atrophy of the stratum malpighii Large nearly round spaces lie close to the epidermis separated from it by only a narrow zone of normal collagen These spaces extend through the upper third of the dermis and are sharply demarcated by collagen bundles arranged circularly around them

They are filled incompletely by a fissured mass of homogeneous appearing material containing a moderate number of nuclei (Fig 75) The material referred to as colloid usually stains eosinophilic with hematoxylin and eosin though to a lesser degree than normal collagen Occasionally however it stains faintly basophilic The fissuring of the colloid is due to fixation and dehydration The nuclei within the colloid are well preserved and represent fibroblasts Elastic tissue stains reveal elastic fibers within the masses of colloid however they are fragmented and fewer in number than in normal collagen

In colloid degeneration of the skin colloid is present not in superficial circumscribed foci but diffusely throughout the dermis (Reuter and Becker)

Differential Diagnosis Differentiation of colloid milium from amyloidosis (see page 274) requires special staining since these two substances greatly resemble each other morphologically and usually stain alike a pale pink with hematoxylin and eosin One may use van Gieson's stain which stains colloid yellow and amyloid pink or methyl violet with which only amyloid is stained

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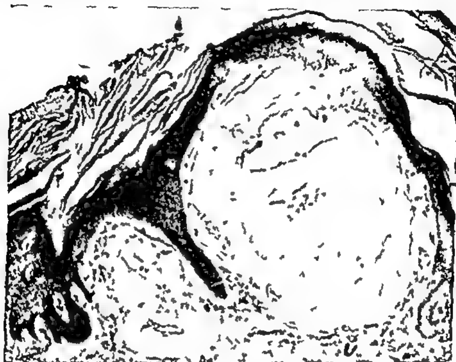


FIG 75 *Colloid milium In the upper dermis separated from the* epidermis by a narrow zone of normal collagen there are two large *round spaces incompletely filled with a fissured mass of homogeneous* material This material represents colloid The colloid contains a moderate number of nuclei (×100)

epidermal region *It is assumed by many that colloid represents a* form of collagen degeneration Prakken has observed that collagen before becoming colloid passes through the stage of basophilic degeneration However it is possible that colloid like amyloid represents a deposit rather than a product of collagen degeneration (Percival and Duthie)

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11

Bacterial Diseases

IMPETIGO

Impetigo may be caused by streptococci or by staphylococci Bullae are the primary lesion in either case In the streptococcal variety, the bullae soon rupture leaving sharply demarcated erosions which be

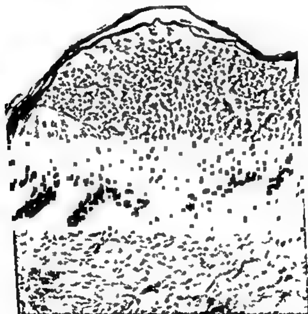


Fig 76 Impetigo A subcorneal vesicle filled mainly with neutrophils is present The epidermis shows spongiosis Many neutrophils are seen migrating through the epidermis (×200)

come covered with heavy, honey colored crusts In the staphylococcal variety the bullae are more durable and dominate the clinical picture Staphylococcal impetigo occurs especially in the newborn (formerly also called pemphigus neonatorum)

Histopathology In both the streptococcal and the staphylococcal variety of impetigo the bulla arises directly beneath the horny layer

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Impetigo Bockhart presents a subcorneal pustule situated in the opening of a hair follicle. The upper portion of the hair follicle is surrounded by a considerable inflammatory infiltrate containing varying numbers of polymorphonuclear leukocytes.

A furuncle presents on histologic examination a perifollicular abscess composed of a dense mass of polymorphonuclear leukocytes with a few lymphocytes. The hair with its follicle and its sebaceous glands is destroyed in the process.

In folliculitis barbae the perifolliculitis is, as a rule, less acute than in furunculosis and does not necessarily result in a perifollicular abscess. Frequently the infiltrate around the follicle contains relatively few polymorphonuclear leukocytes but consists mainly of lymphocytes, plasma cells and histiocytes. Some of the sebaceous glands undergo destruction, but the hair follicles may escape destruction. Foreign body giant cells frequently are present around the hair follicles and the remnants of sebaceous glands. In many cases instead of being limited to the vicinity of the follicles, the infiltrate extends through the entire upper dermis.

FOLLICULITIS KELOIDALIS (DERMATITIS PAPILLARIS CAPILLITII)

Folliculitis keloidalis represents a chronic folliculitis *resulting in* keloidal scarring. It occurs on the nape of the neck *in men*. *In early* cases one observes follicular papules, pustules and occasionally *abscesses*. *The* lesions are replaced gradually by fibrous *nodules*.

Histopathology. Early lesions show the same histopathologic picture as that of a *furuncle*. Older lesions show chronic *granulation* tissue containing n[illegible] ytes and fib[illegible] around [illegible] ultimately the histologic picture is the same as in keloid, showing bundles of hypertrophic and sclerotic collagen.

HIDRADENITIS SUPPURATIVA

Hidradenitis *suppurativa represents* a chronic staphylococcal infection of the apocrine *glands in the* axillary or the pubic regions. Early lesions consist of red, *tender nodules*, which become fluctuating and finally discharge *pus*. *Ulcers may develop* and healing takes place with considerable scarring.

Histopathology. The *infection enters by* way of the follicles and excretory ducts of the apocrine *glands*. *The* earliest cellular reaction is encountered in the subcutaneous tissue within and around the

(see "Classification of Bullae," page 64) The bulla contains fibrin polymorphonuclear leukocytes and some lymphocytes (Fig 76) With Giemsa's or Gram's stain, groups of cocci can be recognized within the bulla They may lie extracellularly or within neutrophils

The stratum malpighii underlying the bulla shows spongiosis many neutrophils can be seen migrating through it The upper dermis contains a moderately severe inflammatory infiltrate of neutrophils and lymphocytes

At a later stage, when the bulla has ruptured, the horny layer is absent, and a crust composed of fibrin and neutrophils may be found resting on the stratum malpighii

ERYSIPELAS

Erysipelas is a localized acute inflammation of the skin caused by streptococci It is characterized by the presence of well demarcated dusky red areas with or without edema and vesiculation A typical sign is the advancing red, raised and indurated border

Histopathology. The dermis shows marked edema and dilatation of lymphatics and capillaries *When the edema is intense subepidermal bullae may be present* There is a marked diffuse infiltrate extending throughout the dermis and, occasionally, into the subcutaneous fat It is composed chiefly of polymorphonuclear leukocytes and some lymphocytes If sections are stained with Giemsa's or Gram's stain, streptococci are found chiefly in the lymphatics, but also distributed in the tissue

FOLLICULITIS (IMPETIGO BOCKHART, FURUNCLE, FOLLICULITIS BARBAE)

Pustular folliculitis may occur in three forms as impetigo Bockhart, as furuncle and as folliculitis barbae (sycosis vulgaris) All three are caused by staphylococci

Impetigo Bockhart represents a superficial pustular folliculitis and is characterized by an eruption of pustules many of which are pierced by a hair

A furuncle is a deep seated folliculitis leading to a *perifollicular* cellulitis and *terminating in suppuration and necrosis*

Folliculitis *barbae is a deep seated folliculitis* peculiar to the bearded region At first there are follicular papules and pustules which are followed by diffuse erythema crusting and infiltration of the skin Abscesses may be present or absent

Histopathology. These three diseases cannot always be differentiated on a histologic basis

Osler nodes are erythematous slightly raised tender intracutaneous nodes averaging 5 mm in size They occur most frequently on the fingertips and as a rule last 4 or 5 days

Janeway lesions are small macular or papular lesions measuring from 1 to 4 mm in diameter They are usually red but may be partially hemorrhagic They occur most commonly on the palms and the soles Unlike Osler nodes they are never tender

Histopathology The petechiae show the histologic picture of an inflammatory purpura (see page 127) presenting severe vasculitis in addition to the extravasation of red cells One observes marked endothelial proliferation of capillaries leading to narrowing or even obliteration of the lumina An infiltrate composed of polymorphonuclear leukocytes lymphocytes and histiocytes surrounds and invades the capillaries Streptococci have never been found in the lesions (Merklen and Wolf Cornil Mosinger and Jouve)

The Osler nodes show involvement not only of the capillaries but also of the dermal arterioles and venules which show intense endothelial proliferation and not infrequently partial or complete occlusion of their lumina by secondary thrombosis A dense infiltrate of polymorphonuclear leukocytes lymphocytes and histiocytes is present in the walls of the vessels and in the perivascular areas The center of the node may show necrosis Extravasation of erythrocytes is absent (Cornil Mosinger and Jouve)

The Janeway lesions resemble the petechiae in their histologic appearance except that extravasation of erythrocytes is less evident

MENINGOCOCCEMIA (WATERHOUSE FRIDERICHSEN SYNDROME)

In fulminating septicemic infections with *Neisseria meningitidis* purpura is common Death may occur within from 12 to 24 hours with few or no signs of meningeal involvement On autopsy hemo-rhages [illegible]

Ma [illegible]

[illegible] ouse Friderichsen syndrome occurs in septicemic infections with organisms other than *Neisseria meningitidis* such as *Streptococcus hemolyticus* and *Pseudomonas aeruginosa* (*B pyocyaneus*)

Histopathology The purpura of meningococcemia is caused by degeneration and inflammatory invasion of the walls of blood vessels (vasculitis) (see page 127) The vessels are dilated engorged with blood and frequently thrombosed The endothelial cells are swollen and desquamating and the vessel walls show necrosis Polymorphonu

lumina of apocrine glands The infection extends through the subcutaneous fat by way of the lymphatics to other apocrine glands as well as to eccrine glands The lymph vessels are distended and contain many leukocytes and clumps of cocci In the early stage, the infiltrate is composed predominantly of neutrophils Later on, lymphocytes and plasma cells predominate and foreign body giant cells may be present The upper parts of the dermis and the epidermis are not involved until extensive destruction has occurred throughout the subcutis

PYODERMA GANGRENOSUM (CHRONIC UNDERMINING BURROWING ULCER)

Pyoderma gangrenosum begins with cutaneous abscesses which break down, forming ulcers The ulcers spread peripherally The advancing border of the ulcers is purplish red, edematous and undermined The condition is associated not infrequently with ulcerative colitis

Histopathology. The histologic appearance is not diagnostic In the region of the ulcer, the epidermis is absent The upper dermis shows necrosis and is permeated by an acute inflammatory infiltrate Farther down, the infiltrate is chronic inflammatory, granulomatous in nature, consisting of lymphocytes, neutrophils, plasma cells histiocytes and fibroblasts Epithelioid cells and foreign body giant cells

The infiltrate may extend deeply into the subcutaneous layer In areas of healing, fibrosis occurs

The epidermis at the edge of the ulcer often shows considerable proliferation, so that the histologic picture of *pseudo epitheliomatous hyperplasia* (see page 334) may result Intra epithelial abscesses *may occur in this region*

Differential Diagnosis. Any ulcer, whatever its genesis may present *the histologic picture just described* If the biopsy specimen is taken from an area in which the epidermis shows marked hyperplasia *differentiation from bromoderma* may be impossible, since bromoderma too shows marked epithelial hyperplasia and intra epithelial abscesses

SUBACUTE BACTERIAL ENDOCARDITIS

Three types of cutaneous lesions may occur in subacute bacterial endocarditis petechiae, Osler nodes and Janeway lesions (Libman and Friedberg)

In old lesions, no pustulation remains and the greatly thickened horny layer consists largely of fully keratinized cells with only a few areas of parakeratosis (Herold and Smith)



Fig 77 Keratosis blennorrhagica late stage Low magnification There is a very thick parakeratotic horny layer (H L) permeated by numerous neutrophils The upper stratum malpighii is the seat of a spongiform pustule (S P) The spongiform appearance is caused by the preservation of the cellular membranes of epidermal cells within the pustule There are elongation of the rete ridges and edema of the papillae (×100)

Gonococci can be demonstrated only rarely in the l

cases and in smears from the lesions in 5 Only one case is on record in which gonococci were recovered on direct culture of the lesions (Margolin) It is likely that many of the cases reported in the literature as keratosis blennor

clear leukocytes are found in the damaged vascular walls as well as perivascularly Large and small areas of hemorrhage are present in the tissue

Meningococci can be demonstrated in the cytoplasm of endothelial cells and polymorphonuclear leukocytes They are also found free in the lumina of vessels and in the perivascular spaces In addition the thrombi frequently contain meningococci Although these organisms can be recognized in routine stains, they are best demonstrated by Giemsa stain

KERATOSIS BLENNORRHAGICA (GONORRHEAL KERATOSIS)

Keratosis blennorrhagica occurs in chronic gonorrhea usually in *association with urethral discharge and polyarthritis* The lesions have a predilection for the palms, the soles, and the glans penis Early lesions are represented by pustules Gradually, the lesions become covered with thick, horny crusts Confluence of neighboring lesions leads to the formation of extensive horny excrescences, which have been compared with mountain ranges on a relief map

Reiter's disease, which in typical cases consists of the triad of urethritis, arthritis and conjunctivitis, may present cutaneous lesions identical with those of keratosis blennorrhagica, but gonorrhea is *not the cause of the disease*

Histopathology. The first histologic changes consist of the appearance of an acute inflammatory infiltrate in the dermis and the formation of pustules in the uppermost epidermis (Carr and Friedman, Epstein and Chambers) As a rule, the pustules are spongiform (Fig 77) (Kogoj) as in acrodermatitis continua and in impetigo herpetiformis (see pages 102 and 104) The spongiform appearance of the pustules is caused by the presence of neutrophils inside of edematous degenerated epidermal cells whose cellular membranes traverse the pustule like the network of a sponge (Fig 78)

Simultaneously with or shortly after the formation of the pustules the rete ridges become elongated At this stage, the histologic picture is indistinguishable from that of acrodermatitis continua

However, as the lesions age the parakeratotic horny layer thickens to a degree that is not observed in acrodermatitis continua and is typical of keratosis blennorrhagica The greatly thickened horny layer is the anatomic substrate for the mountain relief appearance of the lesions observed clinically The horny layer may measure several millimeters in thickness It consists of parakeratotic cells intermingled with neutrophils (Fig 77)

In old lesions no pustulation remains and the greatly thickened horny layer consists largely of fully keratinized cells with only a few areas of parakeratosis (Herold and Smith)



Fig. [illegible] Keratosis blennorrhagica late stage Low magnification There is a very thick parakeratotic horny layer (H L) permeated by numerous neutrophils The upper stratum malpighii is the seat of a spongiform pustule (S P) The spongiform appearance is caused by the preservation of the cellular membranes of epidermal cells within the pustule There are elongation of the rete ridges and edema of the papillae (×100)

Gonococci can be demonstrated only rarely in the lesions of keratosis blennorrhagica Veale and Singletary found that out of a total of 115 cases reported in the literature Gram negative diplococci were demonstrated in tissue sections in 6 cases and in smears from the lesions in 5 Only one case is on record in which gonococci were recovered on direct culture of the lesions (Margolin) It is likely that many of the cases reported in the literature as keratosis blennor

rhagica were nongonorrheal and represented instances of Reiter's disease (Kuske)

In REITER'S DISEASE *the histologic picture is the same* as in keratosis blennorrhagica (Lever and Crawford)

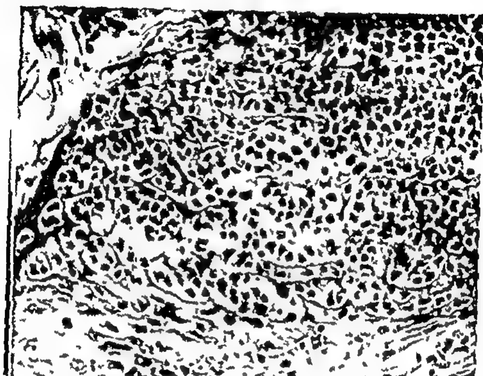


FIG 78 Keratosis blennorrhagica Late stage High magnification of Figure 77 The spongiform nature of the pustule is well apparent (×400)

TUBERCULOSIS

When a normal not previously infected guinea pig is inoculated intracutaneously with an adequate dose of tubercle bacilli a hard *nodule develops at the site of inoculation* after from 8 to 12 days The nodule soon ulcerates The regional lymph nodes become enlarged and sometimes ulcerate (Ghon complex) Histologic examination of the primary ulcer from 10 to 14 days after inoculation reveals a marked inflammatory response with many polymorphonuclear leukocytes and tubercle bacilli During the next 2 weeks the histologic picture changes Lymphocytes and epithelioid cells appear and replace the polymorphonuclear leukocytes Distinct tubercles or tuberculoid structures develop at the site of inoculation, and in the regional lymph nodes as well within 3 to 4 weeks after the inoculation Simultaneously with the appearance of epithelioid cells the number of tubercle bacilli decreases rapidly (Sulzberger)

A typical tubercle consists of an accumulation of epithelioid cells surrounded by a wall of lymphocytes Usually a few Langhans giant cells are present among the epithelioid cells The epithelioid cell center of the tubercle may show various degrees of caseation If such typical tubercles are present, one speaks of a tuberculous infiltrate Frequently, however, in tuberculosis one does not find typical tubercles but only irregular accumulations of epithelioid cells within an inflammatory infiltrate, with or without caseation, and with or without Langhans giant cells In that case, one speaks of a tuberculoid infiltrate

It is important to realize that a tuberculous, and particularly a tuberculoid infiltrate does not necessarily mean tuberculosis Either may occur in many other diseases, particularly syphilis, leprosy and several of the deep fungus infections The Jadassohn Lewandowsky law states that, wherever micro organisms or their products are being overcome or neutralized by the local immunobiologic reactions, tubercles or tuberculoid structures have a tendency to appear

Of interest is the work of Sabin, who found, by intracutaneous injections of various fractions of tubercle bacilli, that the protein fraction evokes the necrotizing and lymphocytic response and the phospholipid fraction evokes the epithelioid cell response

The histologic diagnosis of the various types of cutaneous tuberculosis is dependent on the correlation of the degree of caseation necrosis the amount of inflammatory infiltrate, the degree of vascular changes and the relationship of the tubercles to blood and lymph vessels

Caseation necrosis is so called because of the cheesy macroscopic appearance of the affected tissue Microscopically, areas of caseation necrosis show complete loss of their architectural outline One observes eosinophilic granular material in which unless the caseation necrosis is far advanced some nuclei are still present However most of the nuclei show pyknosis (shrinkage) or karyorrhexis (fragmentation) In local tuberculous infections, caseation necrosis is caused by the action of bacterial toxins alone In hematogenous infections, obliterative changes in the vessels are responsible in part If any marked inflammatory infiltrate is absent in lesions of tuberculosis, it is indicative of either a relative resistance of the host or of an attenuated infection

No generally accepted classification of tuberculosis of the skin exists The classification presented in Table 3 is based on the classifications offered by Montgomery and by Laymon and Michelson

TABLE 3—CLASSIFICATION OF TUBERCULOSIS OF THE SKIN

	AMOUNT OF CASEATION
1 *Primary tuberculosis*	
a Localized infection tuberculous chancre	Considerable
b Hematogenous disseminate infection generalized miliary tuberculosis of the skin	Considerable
2 *Reinfection tuberculosis*	
a Localized infection	
(1) Lupus vulgaris	Slight
(2) Tuberculosis verrucosa cutis	Moderate
(3) Scrofuloderma	Considerable
(4) Tuberculosis cutis orificialis	Considerable
b Hematogenous disseminate infection tuberculids	
(1) Micropapular tuberculid either purely papular or rosacea like (Lewandowsky)	None
(2) Lupus miliaris disseminatus faciei	Slight
(3) Papulonecrotic tuberculid	Considerable
(4) Lichen scrofulosorum	None
(5) Erythema induratum	Considerable

1 PRIMARY TUBERCULOSIS

Primary infection with tuberculosis usually takes place in childhood It occurs only very rarely on the skin In the vast majority of cases, *it presents itself in the lung as the so called Ghon complex or* primary complex This consists of a small, caseous lesion at the periphery of one lung with caseation of the regional hilar lymph nodes The Ghon complex does not become chronic It either heals or extends rapidly Extension may be by continuity or by hematogenous dissemination In the latter case, miliary tuberculosis may develop

A TUBERCULOUS CHANCRE

Primary infection of the skin with tuberculosis is more apt to occur in children but may be seen in adults (Michelson, 1935) The cutaneous lesion usually consists of a crust covered ulcer It is referred to as tuberculous chancre or primary inoculation tuberculosis of the skin The regional lymph nodes are enlarged and may or may not suppurate and produce draining sinuses

Histopathology. The histologic development of the lesion is very much like that observed in experimental cutaneous inoculation of the guinea pig with tubercle bacilli (see page 174) During the early

of the disease the histologic picture is that of a banal, acute,

necrosis After from 3 to 6 weeks, a more specific histologic picture develops Epithelioid and Langhans giant cells are then present, though typical tubercles do not form, as a rule Caseation necrosis remains a prominent feature At this stage, the number of tubercle bacilli is so greatly decreased that it may be impossible to demonstrate them in histologic sections and the only proof of their presence is through positive animal inoculation experiments Simultaneously with the decrease in the number of tubercle bacilli in the lesion, the tuberculin test, previously negative, becomes positive The histologic picture in the regional lymph nodes is identical with that of the cutaneous lesion (O Leary and Harrison)

B GENERALIZED MILIARY TUBERCULOSIS OF THE SKIN

The cutaneous lesions are usually papules but may be vesicles or pustules They tend to break down and form small ulcers

Histopathology. In early lesions, one observes a nonspecific inflammatory infiltrate with foci of necrosis but without tuberculoid reaction Numerous tubercle bacilli are found within the blood vessels and in the foci of necrosis At a later stage, tuberculoid formations may be encountered (Wise)

2 Reinfection Tuberculosis

The immunity acquired by the primary infection almost always protects at least for several years After such a latent period reinfection may occur Reinfection tuberculosis usually is mono-organic, so that in cases in which the skin is affected other organs are, as a rule, free from active tuberculosis As in primary tuberculosis, the infection of the skin may be localized or disseminate

A LOCALIZED INFECTION

In localized infections one may find, depending on the virulence of the bacilli and the degree of resistance of the host, either a slight amount of caseation, as in lupus vulgaris, a moderate amount of caseation as in tuberculosis verrucosa cutis, or a considerable amount of caseation as in scrofuloderma and tuberculosis cutis *orificialis*

(1) *Lupus Vulgaris*

In lupus vulgaris the lesions, which are found most commonly on the face consist of sharply demarcated, reddish brown patches containing pinhead sized, deep-seated nodules If the blood is pressed

out of the skin by pressure with a glass slide (diascopy) the nodules stand out clearly as yellowish brown macules Because of their yellowish brown color, the nodules are referred to as apple jelly nodules. In the course of time as a rule, the affected areas become atrophic with contraction of the tissue However some areas may show verrucous thickening (lupus vulgaris verrucosus) or superficial ulceration Squamous cell carcinoma may develop at the margin of the ulcers



Fig 79 Lupus vulgaris Low magnification There are several tubercles The large tubercle in the center shows slight caseation necrosis (×100)

Histopathology Typical tubercles with epithelioid cells giant cells and a peripheral zone of lymphocytes are present Caseation necrosis within the tubercles is slight and may be absent (Figs 79 and 80) The amount of inflammatory infiltrate composed of lymphocytes and plasma cells varies In some cases the inflammatory infiltrate dominates the histologic picture so that one has to search for occasional tubercles, in other cases it is slight

The infiltrate of lupus vulgaris is most pronounced in the upper dermis but in some areas may extend into the subcutaneous layer. It causes destruction of the cutaneous appendages. In areas of heal ing, extensive fibrosis occurs.

Secondary changes in the epidermis are common. In some areas the epidermis may show acanthosis, hyperkeratosis and even papil

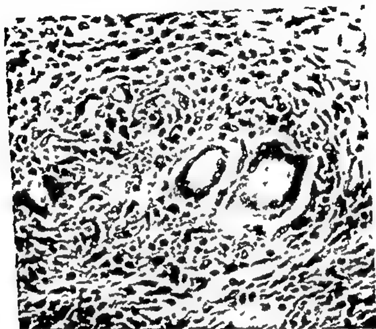


FIG. 80. Lupus vulgaris. High magnification of *Figure 79*. A tubercle containing several Langhans giant cells is shown. The nuclei of the giant cells lie in horseshoe arrangement. (×400)

lomatosis (lupus vulgaris verrucosus). In other areas, by the pressure of the infiltrate, atrophy and even destruction of the epidermis may occur, resulting in ulceration and secondary pyogenic infection. At the margin of such ulcers pseudo-epitheliomatous hyperplasia and, in some instances, squamous-cell carcinoma may be found.

Tubercle bacilli are present in such small numbers that their pres ence can hardly ever be demonstrated by staining methods. Guinea pig inoculation, on the other hand, usually gives a positive result.

Differential Diagnosis. Differentiation from sarcoidosis may be very difficult and occasionally is impossible. No absolute histologic criterion exists by which the two diseases can be differentiated with certainty. As a rule, however, the infiltrate in sarcoidosis tends to

lie in scattered islands throughout the dermis while in lupus vulgaris the infiltrate tends to be compact and to lie mainly in the upper dermis Furthermore sarcoidosis usually shows much less lymphocytic reaction more fibrosis around the nests of epithelioid cells a smaller number of giant cells and complete absence of necrosis (Ronchese) The epidermis in sarcoidosis is either normal or shows pressure atrophy while in lupus vulgaris in addition to atrophy there may be areas of ulceration acanthosis and pseudo epitheliomatous hyperplasia However the only laboratory procedure by which the two diseases can be differentiated with certainty is guinea pig inoculation which usually is positive in lupus vulgaris always negative in sarcoidosis

For a discussion of swimming pool granuloma which is thought by some to be an inoculation lupus vulgaris see page 142

(2) Tuberculosis Verrucosa Cutis (Including Verruca Necrogenica)

This form of tuberculosis represents an infection of a nearly immune skin with virulent tubercle bacilli The lesions of which there may be one or several consist of verrucous hyperkeratotic areas surrounded by an inflammatory border Crusts may be intermingled with the keratotic material Frequently pus may be expressed from fissures within the verrucous lesion

Histopathology The histologic picture shows acanthosis hyperkeratosis and papillomatosis of the epidermis Beneath the epidermis there is an acute inflammatory infiltrate of polymorphonuclear leukocytes and lymphocytes with abscess formation In the middle portion of the dermis one usually finds typical tubercles with a moderate amount of caseation necrosis At times however only a nonspecific inflammatory infiltrate is present Tubercle bacilli are more numerous than in lupus vulgaris and therefore occasionally can be demonstrated histologically (Montgomery)

(3) Scrofuloderma (Tuberculosis Cutis Colliquativa)

Scrofuloderma may originate in the subcutaneous tissue frequently however it represents a direct or lymphatic extension to the skin of an underlying tuberculous focus located usually in a lymph node or bone The lesion becomes first manifest as a bluish red painless swelling which suppurates and later breaks down to form an ulcer with irregular undermined bluish borders

Histopathology The center of the lesion shows nonspecific abscess formation with ulceration of the epidermis At the periphery how

ever one sees tubercle formation with marked caseation necrosis and a considerable amount of chronic inflammatory reaction (Fig 81) The number of tubercle bacilli is usually sufficient to enable one to find them in sections stained after Ziehl Neelsen (Michelson, 1924)

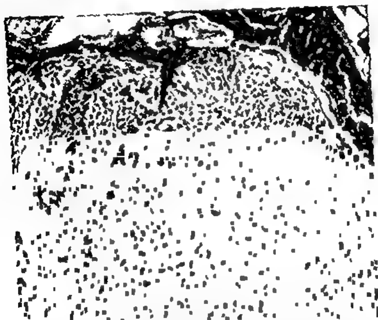


FIG 81 Scrofuloderma Margin of an ulcer On the right side of the photograph one observes necrosis of epidermis and dermis In the center are tuberculoid structures On the left the infiltrate is composed of lymphocytes and plasma cells (X200)

Differential Diagnosis For differentiation from erythema induratum see page 186 and from gummatous syphilis, see page 215

(4) Tuberculosis Cutis Orificialis

The lesions are shallow ulcers with a granulating base, occurring about the mucous orifices of patients with virulent internal tuberculosis.

Histopathology The histologic picture may show merely an ulcer surrounded by a nonspecific inflammatory infiltrate. In most instances however one finds tubercle formations with caseation necrosis deep in the dermis The epidermis at the margin of the ulcer may show hyperplasia Tubercle bacilli usually can be demonstrated in the sections even when the histologic appearance is nonspecific

B HEMATOGENOUS DISSEMINATE INFECTION TUBERCULIDS

Tuberculids are caused by a hematogenous dissemination of tubercle bacilli in patients possessing a rather high immunity to tuberculosis Because of the high immunity, the bacilli are rapidly destroyed in the skin and therefore are usually not demonstrable in sections or by animal inoculation Although, naturally the hematogenous dissemination must take place from an internal focus often this focus cannot be found Clinically as well as histologically, transitions between the various forms of tuberculids occur not infrequently

(1) Micropapular Tuberculid (Including Rosacea like Tuberculid of Lewandowsky)

The eruption is limited to the face and consists of numerous small slightly indurated but not elevated papules of about pinhead size



FIG 82. Micropapular tuberculid (rosacea like tuberculid of Lewandowsky) In the center there is an island of epithelioid cells with only a slight admixture of lymphocytes This picture is indistinguishable from that of sarcoid (×100)

Some of the patients present in addition a diffuse erythema of the face To these cases the term rosacea like tuberclid of Lewandowsky has been applied

Histopathology Histologically the papules usually show islands of epithelioid cells with only a few lymphocytes and few or no giant cells they thus present a picture indistinguishable from that of sarcoidosis (Fig 82) (Laymon and Michelson) In other cases a moderate admixture of lymphocytes is present so that the appearance resembles lupus vulgaris more than sarcoid (MacKee and Sulzberger) Caseation necrosis is absent as a rule occasionally one finds slight central necrosis in the tubercles (Wile and Grauer)

Since the papular type of acne rosacea may show the same histologic picture as the rosacea like tuberculid of Lewandowsky (Miescher Laymon) (see page 124) the latter diagnosis should never be made on the basis of the histologic findings alone but only when the following additional criteria exist (1) presence clinically of minute lupoid nodules and (2) concomitant evidence of tuberculosis such as pulmonary tuberculosis or a high *degree of tuberculin* sensitivity (Laymon) The possibility exists that all cases of rosacea like tuberculid are instances of acne rosacea and that cases of micropapular tuberculid without rosacea like features represent miliary sarcoidosis

(2) *Lupus Miliaris Disseminatus Faciei*

Lupus miliaris disseminatus faciei occurs on the face only The eruption consists of firm elevated discrete papules *occurring singly* or in groups

[illegible]

[illegible] lupus vulgaris although in the latter caseation is less pronounced

Lichenoid Tuberculid A variant of lupus miliaris disseminatus faciei with the same histologic picture has been described by Ockuly and Montgomery under the name lichenoid tuberculid There is a generalized eruption of discrete or grouped erythematous papules with predominance on the extremities and usually no lesions on the face

(3) *Papulonecrotic Tuberculid*

The eruption is not limited to the face as it is in the two preceding types In addition to the face the extremities and the trunk may be affected The lesions consist of indolent inflammatory papules which

come in crops and undergo central necrosis Papulonecrotic tuberculid occasionally occurs simultaneously with erythema induratum

Histopathology One observes a small central area of necrosis involving the superficial dermis and the overlying epidermis The area



Fig 83 Lupus miliaris disseminatus faciei A tubercle showing central caseation is present in the dermis It is surrounded by a moderately severe inflammatory infiltrate (×100)

of necrosis is surrounded by a zone of inflammation which is largely nonspecific but may contain at its periphery tubercles showing a moderate amount of caseation necrosis The infiltrate may extend into the subcutaneous fat The blood vessels in the lower dermis show obliterative endarteritis and endophlebitis with thrombosis and recanalization of their lumina The walls of the vessels may be invaded by inflammatory cells The vascular lesions are responsible for the

superficial necrosis The histologic picture may be called a miniature erythema induratum

(4) *Lichen Scrofulosorum*

The lesions which occur chiefly on the trunk consist of indolent pinhead sized papules Their color varies from that of normal skin to a pale red

Histopathology The infiltrate consists of almost pure epithelioid tubercles with only an occasional giant cell A narrow zone of lymphocytes may or may not be present at the periphery of the tubercles There is no caseation The infiltrate is located in the upper dermis and frequently but not invariably is arranged about hair follicles (Montgomery)

(5) *Erythema Induratum*

Erythema induratum or tuberculosis cutis indurativa is a chronic recurrent eruption occurring on the calves of women In contrast with the other tuberculids the presence of tubercle bacilli has been demonstrated repeatedly in histologic sections and by inoculation of guinea pigs (Montgomery O Leary and Barker) The lesions consist at first of painless deep-seated subcutaneous infiltrations Gradually the infiltrations extend to the surface forming bluish red

I.

[illegible] tuberculoid at least in some areas Sometimes however it is necessary to cut deeper into the block of tissue to find such areas

In areas in which the infiltrate is tuberculoid one finds epithelioid and giant cells occasionally in tubercle arrangement (Fig 85) In areas of nonspecific infiltration one observes predominantly lymphocytes and plasma cells Both types of infiltrates invade between the fat cells and gradually replace them (proliferation atrophy or Wucheratrophie of fat) Caseation necrosis is nearly always present and may be extensive In areas of caseation necrosis the fat cells often are still preserved while the invading infiltrate between them has been supplanted by an amorphous finely granular eosinophilic material in which some pyknotic nuclei are present

Vascular changes are extensive and usually severe All sizes of vessels show proliferative changes The changes are severest in the larger arteries and veins Their walls become infiltrated with round cells and greatly thickened in all coats Thrombosis and obliteration result

(Fig 86) The obliteration results in widespread necrosis and abscess formation The necrosis may extend to the dermis and the epidermis and lead to ulceration

Differential Diagnosis Differentiation from erythema nodosum rarely causes difficulties even though a few small foci of tuberculoid

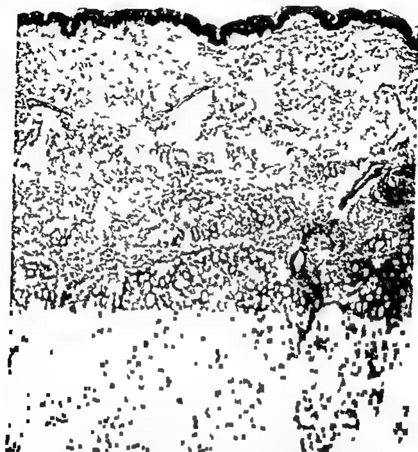


FIG 84 *Erythema induratum Low magnification* The infiltrate is limited to the subcutaneous fat It invades between the fat cells and gradually replaces them (proliferation atrophy of the fat) (×25)

infiltrate may occur in erythema nodosum In the first place the infiltrate is much more massive in erythema induratum than in erythema nodosum, where it usually consists of small scattered aggregates and most important one usually finds at least a few areas of caseation necrosis which never occurs in erythema nodosum Furthermore, extensive tuberculoid infiltration and abscess formation do not occur in erythema nodosum either and if present establish the diagnosis of erythema induratum beyond any doubt Lesions showing a pronounced tuberculoid infiltrate, extensive caseation and ulcera



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proliferation of their walls (×200)

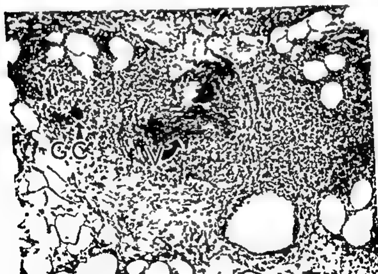


Fig 86 Erythema induratum High magnification A large vessel (V) in the subcutaneous fat is invaded by inflammatory cells and thrombosed At the right of the vessel the inflammatory infiltrate is nonspecific at the left epithelioid cells and a Langhans type of giant cell (G C) are located (×200)

(Fig 86) The obliteration results in widespread necrosis and abscess formation The necrosis may extend to the dermis and the epidermis and lead to ulceration

Differential Diagnosis Differentiation from erythema nodosum rarely causes difficulties even though a few small foci of tuberculoid



Fig 84 Erythema induratum Low magnification The infiltrate is limited to the subcutaneous fat It invades between the fat cells and gradually replaces them (proliferation atrophy of the fat) (×25)

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the center of the epithelioid cell islands If a reticulum stain is employed, one sees a reticulum network surrounding and permeating the islands of epithelioid cells (Fig 89) The network varies in density In most areas, the reticulum fibers surround almost every epithelioid cell, but, in others, the fibers are concentrated at the periphery, leaving the central portions relatively free



... of Sarcoidosis active stage Low magnification There are large islands of epithelioid cells with only a slight admixture of lymphocytes (×50)

In the healing phase, one fin ... rting at the periphery of the isl ... epithelioid cells and the ly ... In such lesions, the gradual transformation of reticulum fibers into collagen ... rs can be ... ent ... pres sha ... lar in

tion may resemble scrofuloderma However scrofuloderma shows no significant vascular changes and usually shows many tubercle bacilli on staining with Ziehl Neelsen s stain

For differentiation from gummatous syphilis see page 215

SARCOIDOSIS

Sarcoidosis is a systemic disease which may affect many organs The skin frequently is involved Four types of cutaneous sarcoidosis are generally recognized Boeck s sarcoid subcutaneous sarcoid of Darier Roussy, lupus pernio of Besnier and erythrodermic sarcoid Boeck s sarcoid the most common type of cutaneous sarcoidosis is charac terized by soft brownish red intracutaneous papules nodules or plaques By central clearing annular lesions may result The lesions only rarely ulcerate Subcutaneous *sarcoid* of Darier Roussy shows subcutaneous nodules which often reach several centimeters in di ameter and do not break down The overlying skin is either of normal color or bluish red Lupus pernio of Besnier presents soft nodules and infiltrated plaques of violaceous color the surface of which shows numerous telangiectases Erythrodermic sarcoid is characterized by large sharply demarcated slightly scaling brownish red patches showing little or no infiltration (Lever and Freeman Wigley and Musso) It might be pointed out that Spiegler Fendt sarcoid is not sarcoidosis but a lymphoid hyperplasia possibly related to lymphoma (see page 491)

Histopathology The histologic picture is essentially the same in all four types of cutaneous sarcoidosis In the skin as in other organs it is characterized by the presence of circumscribed islands of epithelioid cells so called epithelioid cell tubercles

In Boeck s sarcoid the islands of epithelioid cells are located pre dominantly *in the dermis while in Darier Roussy s sarcoid they* are found mainly in the subcutaneous tissue In lupus pernio the histo logic picture differs from that of Boeck s sarcoid only by the pres ence of greatly dilated capillaries in the upper portion of the dermis In the erythrodermic form the infiltrate shows rather small foci of epithelioid cells intermingled with histiocytes and lymphocytes in superficial perivascular arrangement (Lever and Freeman Wigley and Musso)

In active lesions of sarcoidosis the islands of epithelioid cells con tain few Langhans giant cells or none at all (Fig 87) A slight and

is present particu

(Fig 88) Caseation

necrosis is almost always absent Rarely some necrosis is found in

Schaumann, 1936) Numerous organs may be involved (Thomas, Ricker and Clark, Longcope and Freiman) The lymph nodes are frequently, and the tonsils occasionally, involved In the lungs, foci of sarcoidosis are often present and may, on roentgenologic examination, reveal a picture resembling that of miliary tuberculosis or Hodgkin's disease (McCort, Wood, Hamilton and Ehrlich). The



Fig 89 Sarcoidosis active stage Foot's reticulum stain Reticulum fibers surround and permeate the epithelioid-cell islands At the margin of the lesions one can observe the gradual transformation of reticulum fibers into collagen fibers (×100)

spleen may be considerably enlarged The phalanges of the fingers and the toes may show lesions of sarcoidosis, which in roentgenograms look like cysts and formerly were called ostitis cystica of Jungling Histologically, these lesions represent replacement of bone marrow and bone by sarcoid tissue (Ellis). Uveoparotitis of Heerfordt is also a manifestation of sarcoidosis (Pinner, Michelson) In occasional instances, the heart, the kidneys, the gastro-intestinal tract and the central nervous system are the site of lesions (Longcope and Freiman) Involvement of the lungs, if extensive, of the heart or of the central nervous system may cause death

Cause The cause of sarcoidosis is not yet known Some authors regard it as a noncaseating form of *tuberculosis* (Pinner). A few

nated and often calcified (Schaumann 1941) In other cases asteroid inclusion bodies have been found inside of giant cells (Fig 91) (Lever and Freiman) The significance of the Schaumann and the asteroid inclusion bodies is not known Neither is specific for sarcoidosis since Schaumann bodies may occur also in beryllиosis (see page 141) and asteroid bodies have been observed in other granulomas especially in foreign body granulomas



Fig 88 Sarcoidosis active stage High magnification of Figure 87 The island of epithelioid cells is sharply de marcated *A slight lymphocytic infiltrate is present at the margin of the island Giant cells are absent (×200)*

Differential Diagnosis The differentiation of lesions of sarcoidosis from those of lupus vulgaris may be very difficult in cases in which the islands show more than just a slight admixture of lymphocytes (see page 179) *A histologic picture identical with that seen in sarcoi* dosis may occur in the cutaneous granulomas of systemic beryllиosis (see page 141) and in tuberculoid leprosy (see page 195) In the latter however, epithelioid cell islands usually are found invading and de *stroying nerves* in the dermis and the subcutaneous tissue

Systemic Lesions The systemic nature of sarcoidosis at first not recognized, has been established particularly by Schaumann's work

authors have reported the finding of tubercle bacilli in lesions of sarcoidosis (Kyrle Kalkoff and Mohr) It is possible however that in such cases either the diagnosis of sarcoidosis was erroneous or a concomitant tuberculosis existed

If sarcoidosis is due to tuberculosis it is necessary to assume that the tubercle bacilli are quickly killed and disintegrated under the influence of local immune forces Under these circumstances the lipids of the bacillus might be capable of inducing the epithelioid cell response whereas the protein of the bacillus in the absence of hypersensitivity produces no significant necrosis or constitutional reaction (see page 175) Thus the same immunologic situation responsible for the prompt killing of the bacilli might explain the morphologic character of the lesion (Freiman)

LEPROSY

Leprosy is caused by the lepra bacillus *Mycobacterium leprae* an acid fast organism

Three types of leprosy exist lepromatous leprosy tuberculoid (or neural) leprosy and indeterminate leprosy (Canizares Arnold 1949) The lepromatous and the tuberculoid types are definite clinical pathologic bacteriologic and immunologic forms of leprosy They do not occur together in the same patient and transformation of the lepromatous type into the tuberculoid type or vice versa is very rare Indeterminate leprosy represents a transitional stage It may remain indeterminate for a long time and then heal or may develop into lepromatous or tuberculoid leprosy Lepromatous leprosy has a poor prognosis for arrest or recovery while tuberculoid leprosy has a good prognosis for arrest or recovery In lepromatous leprosy the lepromin test is negative because of absence of immunity in tuberculoid leprosy it is positive In indeterminate leprosy the lepromin test may be positive or negative Cases of indeterminate leprosy showing a positive test will probably remain indeterminate or will develop tuberculoid lesions those showing a negative lepromin test [illegible] pro[illegible]

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ch[illegible] [illegible]ltrations of the skin called lepromas These granulomas occur not only in the skin but also in the mucous membranes of the upper respiratory tract the eyes the testes the superficially located nerves and the reticulo-endothelial structures such as the lymph nodes the liver the spleen and the bone marrow Neurologic changes such as anesthesia trophic disturbances and paralysis usually are present Tuberculoid leprosy also called neural or maculo anesthetic leprosy affects mainly the skin and the nerves

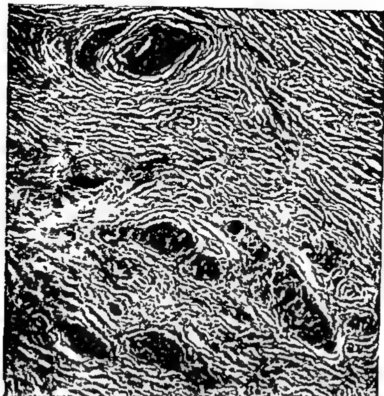


FIG 90 Sarcoidosis healing stage There is considerable fibrosis with progressive obliteration of the epithelioid cells In contrast with early lesions giant cells are numerous (×200)



FIG 91 Sarcoidosis A large giant cell contains an asteroid inclusion body (×400)

authors have reported the finding of tubercle bacilli in lesions of sarcoidosis (Kyrle Kalkoff and Mohr) It is possible however that in such cases either the diagnosis of sarcoidosis was erroneous or a concomitant tuberculosis existed

If sarcoidosis is due to tuberculosis it is necessary to assume that the tubercle bacilli are quickly killed and disintegrated under the influence of local immune forces Under these circumstances the lipids of the bacillus might be capable of inducing the epithelioid cell response whereas the protein of the bacillus in the absence of hypersensitivity produces no significant necrosis or constitutional reaction (see page 175) Thus the same immunologic situation responsible for the prompt killing of the bacilli might explain the morphologic character of the lesion (Freiman)

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The cutaneous lesions consist of sharply circumscribed, erythematous, often hypopigmented patches or flat infiltrations Annular configuration is common The lesions usually are hypoesthetic The peripheral nerves, especially the ulnar nerve, are thickened and palpable Anesthesia, trophic disturbances and paralysis occur just as

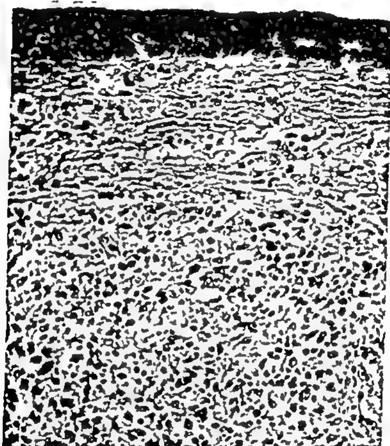


FIG 92 Lepromatous leprosy, early stage The granulomatous infiltrate consists predominantly of histiocytes and lepra cells with foamy cytoplasm (×200)

in the lepromatous type Indeterminate leprosy resembles tuberculoid leprosy in its clinical manifestations

Histopathology Lepromatous leprosy shows a granulomatous infiltrate It is massive in the upper dermis and focal around the arteries, the veins and the nerves in the lower dermis and the subcutaneous fat Histiocytes and lepra cells predominate, but, in addition there are lymphocytes, plasma cells and in older lesions, fibroblasts (Fig 92) Lepra cells, or Virchow cells develop from histiocytes They are large, foamy cells resembling xanthoma cells On staining with fat stains, they are shown to contain lipid which, in contrast to

that found in xanthoma is not doubly refractile (Tilden) On stain

stressed that *Mycobacterium leprae*, unlike *Mycobacterium tuberculosis* is not strongly acid fast Therefore sections must be decolorized

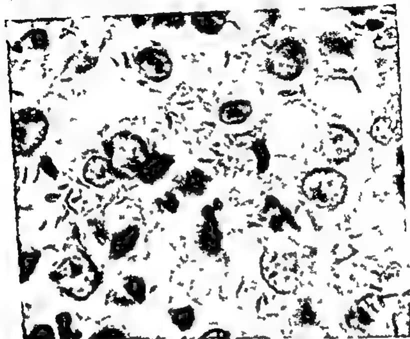


FIG 93 Lepromatous leprosy early stage Ziehl Neelsen stain Numerous lepra bacilli are present In the left center two bundles of bacilli are shown (×800)

... round empty spaces so that they look like large lymphatics (Cowdry) (Fig 94) On staining after Ziehl Neelsen or Fite they may or may not contain large globi of partially degenerated lepra bacilli

Tuberculoid leprosy shows a tuberculoid infiltrate Patients with tuberculoid leprosy have fairly good immunity against the lepra bacillus This explains in accordance with the Jadassohn Lewandowsky law (see page 175) the scarcity or the absence of bacilli and the tuberculoid tissue response Sections may show almost pure epitheli

oid-cell tubercles so that differentiation from sarcoidosis may be difficult *(Fig. 95)*. However, a thorough search usually will reveal invasion and destruction of nerves in the dermis or the subcutaneous tissue by epithelioid-cell tubercles, which never occurs in sarcoidosis. In some cases, the tubercles show a moderate admixture of lymphocytes and contain giant cells. However, caseation necrosis does not occur in the skin. Lepra bacilli may be absent in the lesions of tu-

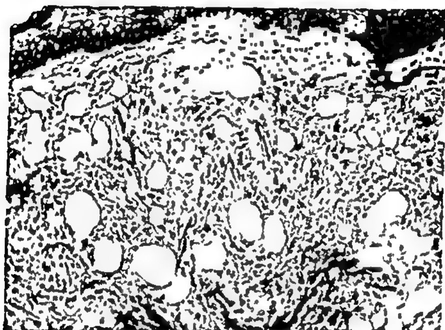


Fig. 94 Lepromatous leprosy, late stage. High magnification. There is some fibrosis. The lepra cells are very large in size and appear as round empty spaces (×200)

berculoid leprosy, but not infrequently they are found in small numbers after prolonged search (Arnold, 1945).

Indeterminate leprosy sho ... around the vessels and the nerves of ... and only with difficulty (Canizares).

Neural Lesions. Lesions in the large peripheral nerves occur in almost every case of leprosy, regardless of type. In all three types, the histologic appearance of the neural lesions corresponds to that of the cutaneous lesions (Pardo Castello, Tiant and Piñeyro). The nerve lesions of lepromatous leprosy show large vacuolated Virchow cells and numerous lepra bacilli. In tuberculoid leprosy, one observes in the nerves an extensive infiltrate of epithelioid-cell tubercles containing few or no bacilli. *However, in contrast with the cutaneous lesions*, caseation necrosis is common. In occasional instances, mas

sive caseation of the tuberculoid lesions with complete destruction of nerve tissue occurs ("colliquative neuritis").



Fig 93 Tuberculoid leprosy Low magnification The infiltrate consists of epithelioid-cell tubercles showing a slight admixture of lymphocytes particularly at their margins Thus the histologic picture is very much like that of sarcoidosis (×100)

DIPHTHERIA OF THE SKIN

The clinical picture of diphtheria of the skin is varied Most commonly encountered are one or several punched-out ulcers covered with a pseudomembrane the removal of which is difficult and followed by profuse bleeding Next in frequency are moist, crusted eczematous lesions which occur particularly in the retro auricular region Other types of lesions occasionally observed include impetiginous, vesicular and bullous lesions (Reiss)

Histopathology. The histologic picture of all forms of diphtheria is nonspecific The ulcerative lesions show destruction of the epidermis and of the upper dermis within the region of the ulcer At the margin of the ulcer, the epidermis is acanthotic The dermis beneath the ulcer shows evidence of acute inflammation The floor of the ulcer is covered with a layer composed of necrotic cells fibrin and numerous neutrophils In some instances, numerous Klebs Loeffler bacilli can be seen in this necrotic layer (Allen) These bacilli have bipolar bodies and tend to lie in palisade like arrangement The finding of such bacilli is suggestive of diphtheria However, since diphtheria bacilli cannot safely be differentiated from pseudo diphtheria bacilli in stained sections, smears and cultures are necessary for the establishment of the diagnosis

The eczematous lesions may show the histologic picture of either an acute, a subacute or a chronic dermatitis The histologic changes thus are identical with those observed in an ordinary bacterial dermatitis (Robert)

ANTHRAX

Anthrax, caused by *Bacillus anthracis*, is characterized by a carbuncle like lesion located usually on an exposed portion of the skin The lesion starts as a papule, enlarges, ulcerates and then becomes covered with a black eschar Frequently, a ring of vesicles is present at the margin of the eschar Marked erythema and edema surround the lesion Suppuration does not occur Pain is characteristically slight or absent Often there is regional lymphadenopathy, which may be painful

Histopathology. At the site of the ulcer, the epidermis is destroyed and the ulcerated surface is covered with necrotic tissue The adjoining epidermis shows spongiosis and occasionally intra epidermal vesicle formation and is invaded by neutrophils There is marked edema of the dermis separating the bundles of collagen and loosening their fibrils Numerous erythrocytes and neutrophils are present throughout the dermis and the subcutaneous tissue However, abscess formation is absent Only few histiocytes can be observed The blood vessels are dilated and their walls show diffuse degenerative changes

Anthrax bacilli are present in large numbers and can be recognized in sections stained with routine stains but are visualized best in sections stained with Gram s stain The anthrax bacillus is a large, rod shaped, square ended Gram positive bacillus, from 6 to 10 microns long and from 1 to 2 microns thick In the tissue, it is usually surrounded by a well defined capsule Anthrax bacilli are found in countless numbers in the necrotic tissue at the surface of the ulcer The dermis also contains numerous bacilli while the subcutaneous

tissue usually contains only a few It is worth noting that phagocytosis of the bacilli by either neutrophils or histiocytes is absent (Lebowich McKillip and Conboy)

TULAREMIA

Tularemia, an infectious disease caused by *Bacterium tularense*, occurs in four types the ulceroglandular the oculoglandular, the glandular and the typhoid types Specific cutaneous lesions occur only in the ulceroglandular type They are of two varieties ulcers and nodes One or several ulcers occur as primary lesions at the site of infection they tend to have a punched-out appearance Cutaneous or subcutaneous nodes form in the small lymph nodes located along the lymph vessels draining the primary lesion they are hard and tender at first but may proceed to suppuration

Histopathology The primary ulcer shows a nonspecific granulation tissue into which are embedded granulomas composed of three zones (1) a central zone of necrosis consisting of finely granular eosinophilic material nuclear fragments and a few erythrocytes (2) an intermediate zone composed of epithelioid cells with a few Langhans giant cells and lymphocytes and (3) an outer zone consisting largely of lymphocytes but containing also some histiocytes plasma cells and extravasated erythrocytes Vascular changes in the outer zone and in the surrounding granulation tissue are conspicuous they consist of proliferation of the endothelial cells and infiltration of the vascular walls by inflammatory cells (Schuermann and Reich) Older lesions may show epithelioid-cell tubercles with only a slight inflammatory reaction and thus may have a sarcoid like appearance *Bacterium tularense* although present does not stain in the sections

The cutaneous lymphatic nodes show like the primary ulcer of tularemia scattered granulomas in which three zones can be recognized

Differential Diagnosis The histologic picture differs from that of tuberculosis by the distinct arrangement in three zones which is rarely seen so clearly in tuberculosis by the presence of vascular changes and by the presence of erythrocytes in the central necrotic zone and the outer lymphocytic zone (Reich) Differentiation from sporotrichosis (see page 230) and lymphogranuloma venereum (see page 252) however may be impossible

CHANCROID

Chancroid caused by the streptobacillus of Ducrey (*Hemophilus ducreyi*) is a venereal disease causing one or several ulcers chiefly

in the genital region The ulcers show little if any induration and tend to have an undermined border Regional lymphadenitis is common and usually terminates in abscess formation (bubo)

Histopathology. The chancroidal ulcer presents a granulomatous reaction which is sufficiently distinct to permit a diagnosis of chancroid in many instances (Heyman, Beeson and Sheldon) The lesion consists of three zones (Sheldon and Heyman) and shows characteristic vascular changes (Pund, Greenblatt and Huie) The surface zone or base of the ulcer is rather narrow and is made up of polymorphonuclear leukocytes fibrin, red blood cells and necrotic tissue Below this is a fairly wide zone of edematous tissue composed mainly of endothelial cells in varying stages of proliferation Newly formed blood vessels are numerous There is marked endothelial proliferation within the vessels, frequently blocking their lumina and leading to thrombosis In addition, there is degeneration of the walls of vessels The third zone is composed of a dense infiltration of plasma cells and lymphocytes

Demonstration of Ducrey bacilli in the tissue by staining with Giemsa's stain, Gram's stain or with polychrome methylene blue is only rarely possible They are most apt to be found as Gram negative coccobacilli between the cells of the surface zone (Sheldon and Heyman)

GRANULOMA INGUINALE

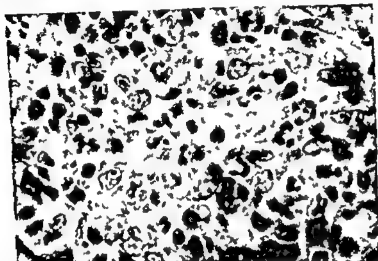
Granuloma inguinale is a venereal disease caused by *Donovania granulomatis,* which *is found in the lesions in the form of* intracytoplasmic inclusion bodies called Donovan bodies The taxonomic position of *Donovania granulomatis* is as yet undecided but it is most likely a bacterium and not a virus It grows well on the chorioallantoic membrane of chick embryos

The lesions occur predominantly in the genital region and consist of sharply demarcated granulomatous areas *which have a livid hue* and bleed easily The border is elevated and often shows a serpiginous outline The lesions spread very slowly by peripheral extension and may attain large size After years the lesions heal with a thick, fibrous, contracted scar In occasional instances squamous cell carcinoma supervenes (Beerman and Sonck Alexander and Shields)

Histopathology The epidermis may be thinned but more often shows acanthosis, which may reach the proportions of pseudo epitheliomatous hyperplasia (Beerman and Sonck) A granulomatous infiltrate is present in the dermis composed predominantly of histiocytes and plasma cells Scattered throughout the otherwise mononuclear infiltrate one finds small abscesses composed of poly

morphonuclear leukocytes (Allen) The number of lymphocytes is conspicuously small

Intracytoplasmic inclusion bodies called Donovan bodies are present within a variable number of histiocytes The parasitized histiocytes or macrophages possess abundant cytoplasm and may measure 20 microns and more in diameter Their cytoplasm has a cystic appearance Within the cystic compartments of the cytoplasm



F g Jf Granuloma ingu nale The granulat on tissue is composed pred m nantly of l t ocytes and plasma cells There is a d ff ise sprin kl g of polymorph nuclear leukocytes Several of the h st ocytes con tain D n van bod es v ith n tl e r cytoplasm (×400)

one sees groups of small round or oval encapsulated bodies meas uring 1 to 2 microns in diameter (Fig 96) In the cross sections of large histiocytes several dozen of such bodies may be observed The Donovan bodies are recognizable in stains with hematoxylin and eosin but are seen best in sections stained with Giemsa s stain In such sections they appear bright red (Alexander and Schoch) When a silver stain is used the Donovan bodies appear black and have the shape of a closed safety pin because of their elongated ovoid shape and intense bipolar staining reaction (Torpin Greenblatt and Pund) The capsule surrounding the Donovan bodies does not stain In addition to their intracellular location a few Dono... be fo... ay be pointed out that it is often

easier to find them in tissue scrapings or tissue imprints stained with Giemsa's or Wright's stain than in fixed tissue sections

Differential Diagnosis The parasitism of histiocytes is strikingly similar to that observed in rhinoscleroma histoplasmosis and leishmaniasis However, the small size of the Donovan bodies and the presence of small abscesses in the infiltrate usually make a differentiation from these diseases possible (See Table 5, page 237)

A difficult problem may be posed by the marked epidermal proliferation present occasionally in granuloma inguinale (Beerman and Sonck) Several biopsies may be necessary to decide whether it represents merely pseudo epitheliomatous hyperplasia (see page 334) or squamous cell carcinoma which occasionally supervenes in granuloma inguinale

RHINOSCLFROMA

Rhinoscleroma is a chronic infectious disease in which the nose the lip and the upper respiratory tract are infiltrated with hard plaques and masses

Histopathology. The granulomatous infiltrate is strikingly rich in plasma cells and contains two peculiar types of cells, the Mikulicz cell and the Russell bodies Because of their presence, the histologic picture of rhinoscleroma is diagnostic

The Mikulicz cell is a very large, round histiocyte measuring up to 100, occasionally even 200, microns in diameter It has a pale reticulated, ill defined cytoplasm and an eccentric nucleus If a bacterial stain such as Giemsa s stain is used one finds within the cytoplasm of many Mikulicz cells as well as in their vicinity many bacilli called *Klebsiella rhinoscleromatis* or Frisch bacilli (Fig 97) They are short, Gram negative rods measuring 2 by 5 microns in length and are surrounded by a narrow gelatinous capsule (called gloea) It is not certain that the disease is caused by this organism

The Russell bodies are elliptic formations, measuring from 20 to 40 microns in diameter Thus, they are smaller than a Mikulicz cell but still twice as large as a normal plasma cell They have a homogeneous, brilliant red light refractile cytoplasm and no nucleus (Fig 98) They form within plasma cells as a result of their degeneration and finally are expelled (see page 37)

The amount of cellular infiltration varies with the age of the lesion Early lesions show considerable infiltration by numerous plasma cells and lymphocytes with occasional histiocytes and eosinophils, many Russell bodies are present but only few Mikulicz cells Gradually, the number of Mikulicz cells increases to such extent that they predominate the histologic picture giving the section a

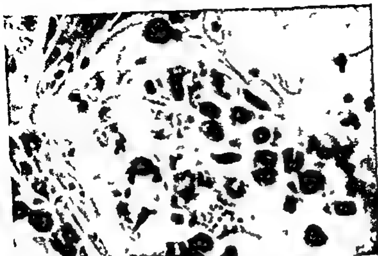


Fig 97 Rh noscleroma G emsa sta n There are se eral M k il cz cells the cytoplasm f wl cl s pale ret culated and ill-define l One M kul cz cell conta ns n its cytoplasm many Frisch bacilli wh ch appear l ere as small ro ind deeply sta n ng bod es (×900)

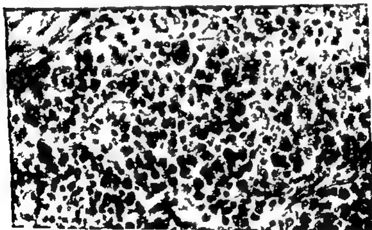


Fig 98 Rh noscleroma The infiltra e conta ns many plasma cells and one Rus ell body The Russell body is larger than the other cells in the infiltrate It has a homogeneous br ll ant red refract le cytoplasm (×400)

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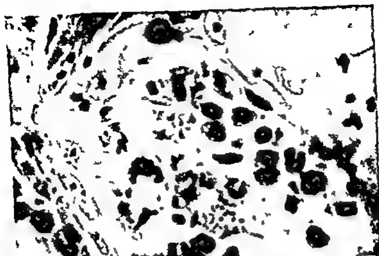


Fig 97 Rhinoscleroma Giemsa stain There are several Mikulicz cells the cytoplasm of which is pale reticulated and ill-defined One Mikulicz cell contains in its cytoplasm many Frisch bacilli which appear here as small round deeply staining bodies ($\times$900)

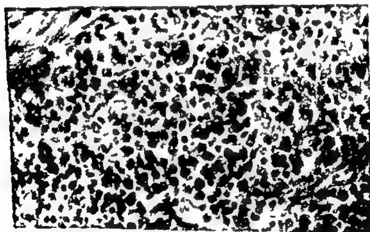


Fig 98 Rhinoscleroma The infiltrate contains many plasma cells and one Russell body The Russell body is larger than the other cells in the infiltrate It has a homogeneous brilliant red refractile cytoplasm ($\times$400)

foamy, lacelike appearance Finally fibrosis replaces the Mikulicz cells (Kline and Brody)

Differential Diagnosis Parasitized histiocytes are observed also in cutaneous leishmaniasis histoplasmosis and granuloma inguinale For their differentiation see cutaneous leishmaniasis (page 235 and Table 5 page 237) Russell bodies are not found in these three diseases and *therefore are of considerable diagnostic value* However they are not specific for rhinoscleroma because they may occur in other diseases when an infiltrate rich in plasma cells is present—for instance in syphilis tuberculosis squamous cell carcinoma and mycosis fungoides

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12

Spirochetal Diseases

SYPHILIS

Acquired syphilis may be divided into three stages primary, secondary and tertiary Primary and secondary syphilis comprise the early phase and tertiary syphilis the late phase of the infection During the early phase, the causative organism, *Treponema pallidum* (*Spirochaeta pallida*), often can be demonstrated in the cutaneous lesions by dark-field examination In the late phase, no spirochetes can be demonstrated in the cutaneous lesions

Primary syphilis is characterized by the syphilitic or hard chancre which is usually a single lesion but may be multiple The typical, or Hunterian, chancre is represented by a brownish red, indurated round papule or plaque with an eroded surface Occasionally, the chancre shows ulceration The regional lymph nodes are enlarged

Secondary syphilis is characterized by a more or less generalized eruption, which is composed usually of macules or papules having a brownish red color In the anogenital region, the papules may become large, verrucous and moist, they are then called condylomata lata (They must be differentiated from condylomata acuminata, a variety of verruca, see page 251) In some instances the cutaneous eruption, due to the presence of scaling, resembles psoriasis (psoriasiform syphilid) Occasionally, pustules develop and are followed by heavy crusting (rupial syphilid) Ulceration of lesions in secondary syphilis is very rare and occurs only in severe cases Alopecia syphilitica is characterized by numerous small patches of partial, "moth eaten" alopecia

Tertiary syphilis often shows only a single lesion, but occasionally several lesions A superficial nodular type and a deep, gummatous

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center. Lesions of the gummatous type begin as a soft cutaneous or subcutaneous swelling, which breaks down to form one or several ulcers having a punched out appearance In rare instances, juxta articular nodes occur in tertiary syphilis They are painless, slowly growing, subcutaneous, fibrous nodules, often symmetrically situated

in the vicinity of joints The elbows and the knees are the sites of predilection

Congenital, or prenatal, syphilis shows the same cutaneous manifestations as acquired secondary and tertiary syphilis with the following exceptions first occasionally bullous lesions occur especially on the palms and the soles as a manifestation of secondary syphilis in infants and second juxta articular nodes do not occur

Histopathology The fundamental pathologic changes in syphilis are (1) a predominantly perivascular infiltrate composed of lymphocytes and many plasma cells and (2) endarteritis and endophlebitis In tertiary syphilis one usually finds in addition a tuberculoid infiltrate and caseation necrosis

PRIMARY SYPHILIS In the typical primary lesion the epidermis shows at the margin of the lesion acanthosis Toward the center the epidermis gradually becomes thinner until in the central portion it is entirely absent (Fig 99) An infiltrate composed of lymphocytes and many plasma cells is present in the dermis It is compact in the center while at the margin it consists of individual perivascular islands Both blood and lymph vessels show changes The capillaries and the lymphatics are increased in number and show considerable proliferation of their endothelial cells (Fig 100) The larger blood vessels show proliferation of all their coats and invasion of their walls by the cellular infiltrate Obliteration and thrombosis of the lumina of some of the vessels is common and results in small foci of necrosis Occasionally the lumina of so many vessels are occluded that massive necrosis results In such cases the primary lesion presents itself as an ulcer instead of an erosion

On staining with Levaditi s stain spirochetes usually can be found often in large number They are found throughout the tissue but especially in and around the walls of capillaries and lymphatics

Histologic examination of the regional lymph nodes in primary syphilis may reveal only a nonspecific inflammation, not infrequently however small foci of tuberculoid reaction are encountered in addition (Michelson)

SECONDARY SYPHILIS In secondary syphilis the number of spirochetes seen in sections stained with Levaditi s stain varies with the type of lesion In the macular lesions of early secondary syphilis spirochetes cannot be found as a rule In papular lesions they are seen occasionally In condylomata lata they are al[illegible]

[illegible] superficial capillaries show swell

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Fig 99 Primary syphilis Low magnification The margin of an erosion is shown The epidermis gradually becomes thinner as it approaches the erosion (×100)

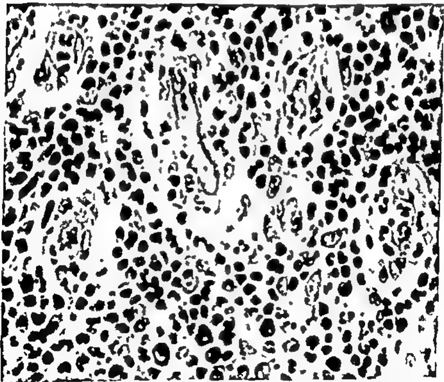


Fig 100 Primary syphilis High magnification of Figure 99 The capillaries are greatly increased in number and show marked prolifera tion of their endothelial cells Many plasma cells are present in the dense infiltrate (×400)

ing of their endothelium and are surrounded by a slight infiltrate of lymphocytes and plasma cells However the number of plasma cells is not sufficiently large to be of diagnostic value

Papular lesions, as a rule, have a diagnostic appearance Not only the superficial but also the deeper vessels of the dermis are involved They show marked endothelial swelling and are surrounded by a pronounced infiltrate (Fig 101) Because of its perivascular coat sleeve like arrangement the infiltrate has a patchy distribution The patchy pattern stands out very clearly in the lower dermis In the upper dermis in addition to the patchy infiltrate there may be ficantly high number of 102) In the differential ie exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe have to be excluded The latter in particular may suggest secondary syphilis because of the patchy distribution of its infiltrate and the presence of many plasma cells but neither chronic dermatitis nor exudative discoid and lichenoid chronic dermatosis shows the marked endothelial swelling of the vessels and the extension of the patchy infiltrate into the lower dermis

Condylomata lata show the same changes in the dermis as the papular lesions In addition the epidermis shows considerable acanthosis with broadening and elongation of the rete ridges intracellular and intercellular edema of the rete cells and migration of polymorphonuclear leukocytes through the epidermis

Psoriasiform secondary syphilis may show epidermal changes similar to those of psoriasis but the dermal infiltrate is ...

... subcorneal pustules The diagnosis of syphilis usually can be made because the lower dermis shows the characteristic infiltrate of secondary syphilis

Ulcerative lesions are rare in secondary syphilis They occur when the larger vessels at the border of the dermis and the subcutaneous tissue become completely occluded by syphilitic endarteritis and endophlebitis (Wile Wieder and Warthin)

... in many instances however no infiltrate is found (essential alopecia) Wile and Belote believe that the latter type of alope... local action of

on endocrine glands or on the autonomic nervous system Meningeal syphilis is common with that type

It is not always possible to assign on the basis of histologic examination, cutaneous lesions of syphilis to either secondary or tertiary syphilis Not infrequently, one finds in lesions which clinically are to be classified as late secondary syphilis an admixture of epithelioid and giant cells On the other hand, lesions of early tertiary syphilis



Fig 101 Secondary syphilis Low magnification The vessels throughout the dermis show endothelial proliferation The cellular infiltrate is located around the vessels in coat sleeve arrangement (×100)

may show the histologic infiltrate of secondary syphilis without any epithelioid and giant cell reaction

Tertiary Syphilis In tertiary syphilis one observes a granulation tissue composed of lymphocytes plasma cells histiocytes, fibroblasts and varying numbers of epithelioid and giant cells Usually but not always the number of plasma cells is prominent The infiltrate is massive in the center but tends to have a perivascular arrangement at the periphery Vascular changes are prominent particularly in the larger vessels They show proliferation of their walls leading to narrowing of their lumina and invasion of their walls by the inflammatory infiltrate Caseation necrosis is frequent It is probable that caseation necrosis is not due to the vascular changes because often the vascular changes are just as severe in areas without caseation as in areas with caseation It seems more likely that caseation represents

an allergic phenomenon caused by alteration in the reactivity of the tissue (Boyd) In the healing stage, lesions of tertiary syphilis show numerous fibroblasts The process ends in fibrosis Tertiary syphilis occurs in the skin in two forms nodular and gummatous

In *nodular tertiary syphilis*, the granulomatous process is limited to the dermis The number of epithelioid and giant cells is small,



ure 101 The perivascular infiltrate contains many plasma cells. (X200)

as a rule Occasionally however these cells are fairly numerous in the center of the lesion They tend to lie without arrangement into real tubercles and giant cells of the foreign body type are more common than those of the Langhans type (Fig 103) Caseation necrosis is usually not extensive and may be absent If extensive, ulceration results

In *gummatous tertiary syphilis* the gran...

... ssive caseation necrosis occurs in the center of the ... giant cells are



Fig 103 Tertiary syphilis nodular type In the center of the field a large island of epithelioid and giant cells is located Most giant cells are of the foreign body type rather than of the Langhans type The infiltrate at the margins contains many plasma cells (×100)

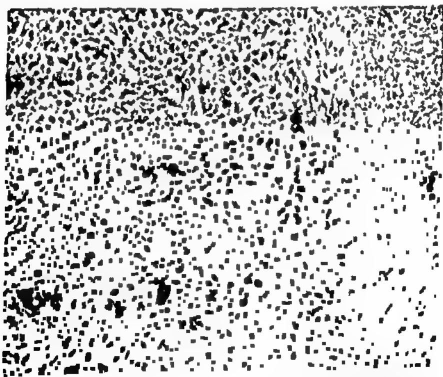


Fig 104 Tertiary syphilis gumma On the left side of the field the
ma cells In the center
nt Most giant cells are
e sees part of the large
of the gumma (×200)

lesion (Fig 103) The epithelioid and the giant cells are located mainly in the vicinity of the areas of caseation Because of the deep extension of the process not only the vessels of the dermis as in nodular tertiary syphilis but also the large vessels of the subcutaneous layer are markedly involved

Differentiation of tertiary syphilis from tuberculosis may be difficult In the absence of caseation, the nodular type may resemble lupus vulgaris and the gummatous type may suggest scrofuloderma or erythema induratum The latter in particular, may be difficult to exclude because it shows obliterative vascular changes similar to those of tertiary syphilis But aside from erythema induratum, vascular changes provide the most important point of differentiation between syphilis and tuberculosis In addition the prevalence of plasma cells and the presence of giant cells of the foreign body type rather than of the Langhans type favor a diagnosis of syphilis

In *juxta-articular nodes* the histologic picture varies with the age of the lesion Early lesions are fairly cellular (Tuta and Coombs) and present embedded in a dense fibrous tissue granulomatous areas composed of epithelioid cells lymphocytes and plasma cells with an occasional Langhans type of giant cell The blood vessels [illegible]

which the histologic picture is the same as just described for early lesions an intermediate zone showing dense fibrous tissue with only few cells and an inner zone showing hyalinized fibrous bands ramifying to form partitions for cystic spaces The cystic spaces contain [illegible]

[illegible] in early nodes the presence of spirochetes (Allen) Jessner as well as Hu Liu Chen and Frazier have succeeded in producing syphilis in rabbits by inoculating them with portions of juxta articular nodes

Congenital Syphilis The histologic changes in the cutaneous lesions of early congenital syphilis are similar to those seen in acquired secondary syphilis Except for the bullous lesions of the palms and the soles The latter may show no plasma cells in the dermal infiltrate but numerous polymorphonuclear leukocytes and a few lymphocytes Obliterative vascular changes are present, however (Fraser)

Syphilis of Internal Organs It is not appropriate to discuss here in detail the histologic appearance of the lesions of syphilis in the

internal organs However it may be pointed out that late syphilis may cause two types of reactions in the internal organs gumma and diffuse interstitial inflammation The latter reaction is more common

The gummata in internal organs show the same histologic changes as those observed in the skin

Diffuse interstitial syphilitic inflammation manifests itself as accumulations of lymphocytes and plasma cells around the small vessels Caseation is usually absent *As a result of the long continued inflammation* there is gradual degeneration of the parenchymatous structures and their replacement by fibrous tissue (Boyd) This type of reaction produces for instance syphilitic hepatic cirrhosis Syphilis of the aorta is also of the diffuse type The process starts around the vasa vasorum of the adventitia The inflammatory infiltrate then extends *along the vasa vasorum into the media In the media one observes foci of inflammatory cells miliary necrosis* and extensive destruction of elastic tissue

General paresis shows perivascular accumulations of lymphocytes and plasma cells in the meninges and in the cortex of the brain In addition there is extensive degeneration of the cortex In contrast to general paresis tabes does not show inflammatory changes The essential lesion is degeneration of the posterior columns of the spinal cord

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13

Fungus Diseases

DERMATOPHYTOSIS (TINEA)

The following are the most important fungi causing superficial fungus infections *Microsporum canis (lanosum)* *Microsporum audouini* *Trichophyton mentagrophytes (gypseum)* *Trichophyton rubrum (purpureum)* *Epidermophyton floccosum* *Trichophyton (Achorion) schoenleini* *Malassezia furfur* and *Nocardia (Actinomyces) minutissima*

Clinically nine types of superficial fungus infections can be recognized (1) tinea capitis (2) tinea barbae (3) tinea corporis (4) tinea cruris (5) dermatophytosis of the feet and the hands (6) onychomycosis (7) favus (8) tinea versicolor and (9) erythrasma

Tinea capitis which occurs almost exclusively in children usually is caused either by *Microsporum canis* or by *Microsporum audouini* The affected hairs tend to break off *Microsporum canis* may evoke pronounced inflammation of the scalp so called kerion Celsi while *Microsporum audouini* usually produces little inflammatory reaction

Tinea barbae rare in the United States is usually caused by *Trichophyton mentagrophytes* It is characterized by a boggy inflammatory infiltration in the bearded region of men

Tinea corporis if caused by *Microsporum canis* manifests itself as multiple annular lesions with an active often vesicular border and central clearing if caused by *Trichophyton mentagrophytes* one finds only one or at the most a few annular lesions showing little or no central clearing if caused by *Trichophyton rubrum* there are fairly sharply demarcated sheetlike areas of erythema with slight scaling

Tinea cruris usually caused by *Epidermophyton floccosum*, produces areas of erythema and scaling with a slightly elevated often vesicular border on the opposing surfaces of the skin between the scrotum and the thighs and in the perineal and the gluteal regions

Dermatophytosis of the feet and the hands usually caused by *Trichophyton mentagrophytes* and occasionally by *Epidermophyton floccosum* is characterized by maceration between and underneath

internal organs However, it may be pointed out that late syphilis may cause two types of reactions in the internal organs gumma and diffuse interstitial inflammation The latter reaction is more common

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the toes and an erythematous scaling and vesicular eruption on the feet and the hands especially the soles and the palms

Onychomycosis caused usually by *Trichophyton rubrum* shows disintegration of the nail substance

Favus rare in this country is caused by *Trichophyton (Achorion) schoenleini* Most commonly it affects the scalp where it produces inflammation with formation of perifollicular crusts called scutula Destruction of the hair ensues Healing takes place with scarring

Tinea versicolor caused by *Malassezia furfur* most commonly affects the upper trunk where one finds areas of brownish discoloration The surface of the discolored areas shows fine branny scaling

Erythrasma caused by *Nocardia minutissima* consists of circumscribed reddish brown slightly scaling patches in the axillae and the groins

Histopathology For the demonstration of fungi in histologic sections the periodic acid Schiff stain of Hotchkiss McManus is of very great value since it stains fungi deeply red while almost all other structures stain a very pale pink (Kligman and Mescon) It should always be used when the presence of fungi is suspected The reason for the strongly positive reaction of fungi to the periodic acid Schiff (PAS) stain is that the cell walls of fungi are composed of mixtures of cellulose and chitin which are rich in polysaccharides (Kligman Mescon and DeLamater)

In histologic sections fungi may present two structures hyphae (or mycelia) and spores Hyphae which are nonreproductive appear as threadlike structures they may be septate or nonseptate The spores which represent reproductive cells appear as round bodies

Tinea of the Glabrous Skin In tinea of the glabrous skin fungi are present in small numbers with the exception of tinea versicolor in which the causative organism *Malassezia furfur* is always present in abundance The fungi are found situated mainly in the upper two thirds of the stratum corneum They may penetrate as far down as the upper layer of the stratum granulosum but they do not occur between living cells In tinea of the glabrous skin except tinea versicolor the fungi occur as short and long segmented and occasionally granular hyphae extending parallel to the surface spores are usually not observed (Peck) In tinea versicolor one sees not only hyphae but also spores

In the absence of fungi no diagnostic picture is presented by fungus infections of the glabrous skin In most instances depending on the degree of reaction of the skin to the presence of fungi one sees the histologic picture of either an acute a subacute or a chronic dermatitis (see p 68) Dermatophytosis of the hands and the feet

titis with intra epidermal ...

TINEA CAPITIS AND TINEA BARBAE In tinea capitis and ... barbae fungi are present not only in the horny layer of the skin but also within and around the hair Kligman, who recently has studied histologically the sequence of events in infections of human hair with *Microsporum canis* and *Microsporum audouini* found that

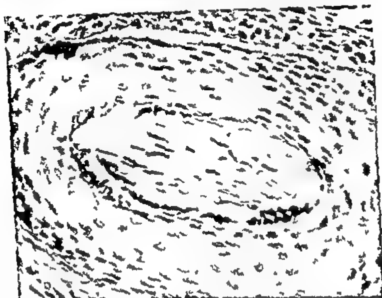


FIG 105 Favus Periodic acid Schiff stain The cross section of a hair follicle is shown The fungus *Trichophyton schoenleini* is present largely as mycelia within and around the hair (×400)

after infection of the scalp surface hyphae grow downward into the follicle on the hair s surface a short distance and then penetrate into the hair Inside the hair they form branches and grow downward but not farther than the exact limit of the zone of keratin synthesis Thus as in the surface epidermis only fully keratinized structures are invaded After the invasion of the hair ectothrix spores are formed by segmentation of external branches of intrapilary hyphae Within the hair however the hyphae form no spores As the infection subsides there is gradual reduction in the quantity of intrapilary hyphae and ectothrix spores

Aside from the presence of fungi the histologic picture in tinea capitis and tinea barbae may be merely one of subacute or chronic dermatitis In kerion Celsi and tinea barbae however folliculitis

the toes and an erythematous, scaling and vesicular eruption on the feet and the hands, especially the soles and the palms

Onychomycosis, caused usually by *Trichophyton rubrum*, shows disintegration of the nail substance

Favus, rare in this country, is caused by *Trichophyton (Achorion) schoenleini* Most commonly it affects the scalp, where it produces inflammation with formation of perifollicular crusts, called scutula Destruction of the hair ensues Healing takes place with scarring

Tinea versicolor, caused by *Malassezia furfur*, most commonly affects the upper trunk, where one finds areas of brownish discoloration The surface of the discolored areas shows fine branny scaling

Erythrasma, caused by *Nocardia minutissima*, consists of circumscribed, reddish brown, slightly scaling patches in the axillae and the groins

Histopathology. For the demonstration of fungi in histologic sections, the periodic acid Schiff stain of Hotchkiss McManus is of very great value since it stains fungi deeply red while almost all other structures stain a very pale pink (Kligman and Mescon) It should always be used when the presence of fungi is suspected The reason for the strongly positive reaction of fungi to the periodic acid-Schiff (PAS) stain is that the cell walls of fungi are composed of mixtures of cellulose and chitin which are rich in polysaccharides (Kligman, Mescon and DeLamater)

In histologic sections fungi may present two structures hyphae (or mycelia) and spores *Hyphae, which are nonreproductive, appear* as threadlike structures, they may be septate or nonseptate The spores which represent reproductive cells appear as round bodies

Tinea of the Glabrous Skin *In tinea of the glabrous skin*, fungi are present in small numbers with the exception of tinea versicolor in which the causative organism, *Malassezia furfur*, is always present *in abundance* The fungi are found situated mainly in the upper two thirds of the stratum corneum They may penetrate as far down as the upper layer of the stratum granulosum, but they do not occur between living cells In tinea of the glabrous skin, except tinea versicolor, the fungi occur as short and long segmented and occasionally granular hyphae extending parallel to the surface spores are usually *not* observed (Peck) In tinea versicolor one sees not only hyphae but also spores

In the absence of fungi, no diagnostic picture is presented by fungus infections of the glabrous skin In most instances, depending on the degree of reaction of the skin to the presence of fungi, one sees the histologic picture of either an acute a subacute or a chronic dermatitis (see p 68) Dermatophytosis of the hands and the feet

TABLE 4.—HISTOLOGIC APPEARANCE OF THE TISSUE AND OF THE FUNGI IN FUNGUS DISEASES

Disease	Histologic Appearance of Tissue	Average Size of Fungus (Microns)	Appearance of Fungus in Tissue
Moniliasis	When invasive nonspecific granulation tissue with abscess formation	4	Hyphae and budding as well as nonbudding yeast cells (spores)
Blastomycosis	Epithelial hyperplasia tuberculoid granulation tissue with formation of small abscesses	10	Thick walled spores in giant cells and tissue Budding forms
Torulosis	Chronic inflammatory infiltrate with extensive caseation	7	Spores with wide gelatinous capsule
Chromoblastomycosis	Like blastomycosis	10	Thick walled, dark brown spores, often in clusters Some cells possess cross walls
Coccidioidomycosis	Granulomatous nodules like blastomycosis except that caseation may occur Subcutaneous abscesses central caseation surrounded by tuberculoid granulation tissue	40	Thick walled spores with granular cytoplasm The larger spores contain endospores
Actinomycosis	Nonspecific granulation tissue with abscess formation	150	Large irregularly lobulated granules with branching filaments and club formation at the periphery
Sporotrichosis	Primary lesion nonspecific granulation tissue Subcutaneous nodules three zones chronic suppurative tuberculoid and syphiloid zone	(5)	Usually, no fungi are seen Occasionally, asteroid forms of spores are present
Histoplasmosis	Chronic granuloma with foci of necrosis	3	Numerous spores surrounded by a clear halo lie in the cytoplasm of large histiocytes

and foreign body giant cells The infiltrate may extend *into the subcutis* As a rule *Candida albicans* is present *only in the stratum* corneum and not in the dermis (Hauser and Rothman)

In the rare instances of abscess formation and ulceration due to *Candida albicans* hyphae as well as spores have been found in the *dermis* especially in the abscesses and their vicinity. The spores measure about 4 microns in diameter. [illegible]

and perifolliculitis (see page 168) frequently are seen At first, an intrafollicular abscess forms The wall of the follicle may then rupture, whereafter the perifollicular tissue becomes the seat of an abscess After discharge of the pus, the abscess cavity begins to fill in with granulation tissue At that stage, epithelioid cells and foreign body giant cells are frequently present, digesting remnants of the follicular epithelium (McCarthy) It may be pointed out that the histologic pictures of tinea barbae and folliculitis barbae (sycosis vulgaris) *are essentially the same (see page 169)*

Favus The fungus is present in the horny layer of the skin, within and *around the hairs* (Fig 105), and in the scutula *In some instances*, the fungus invades the stratum malpighii and even the *dermis (Ormsby and Montgomery)* The scutula are composed at their periphery of well preserved hyphae and spores while in the *center one finds* granular debris and degenerated spores The scutula rest upon an atrophic epidermis The hair follicles underlying the scutula are destroyed The dermis shows a mild to moderately severe inflammatory reaction

MONILIASIS

Candida albicans, the cause of moniliasis, not only is a cutaneous pathogen but also may affect mucosal surfaces, such as the oral *mucosa and the vagina In rare instances Candida albicans may in*fect the lungs or the meninges and cause death

Clinically, cutaneous moniliasis usually is a superficial *infection* characterized by fairly sharply demarcated areas of erythema with or without pustulation The intertriginous areas are predominantly affected Paronychia is common In rare instances granulomatous and hyperkeratotic *lesions form on the face and the scalp of children* so called monilial granuloma and, in adults abscess formation and ulceration may occur

The association of cutaneous and mucosal moniliasis with hypoadrenalism (Talbot Butler and MacLachlan) and *with hypoparathyroidism* (Sutphin Albright and McCune) is known to occur Since this association is often familial, it is *likely that both the endocrine* deficiency and the susceptibility to monilial infection in these cases are due to some defect in the *germ plasm*

Histopathology. Superficial cutaneous moniliasis presents a histologic picture like that *found in subacute or chronic dermatitis* The fungus *elements occur only* in the stratum corneum They consist of hyphae and spores, *some of the latter in a budding stage*

Monilial granuloma shows hyperkeratosis acanthosis and, in the dermis, a dense *infiltrate of lymphocytes, plasma* cells, neutrophils

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In the rare instances of abscess formation and ulceration due to *Candida albicans*, hyphae as well as spores have been found in the dermis especially in the abscesses and their vicinity The spores measure about 4 microns in diameter, have a distinct capsule and

are Gram positive. They often lie in clusters and budding forms are occasionally seen The hyphae are slender rods and have a beaded or segmented appearance (Rockwood and Greenwood, Danbolt)

NORTH AMERICAN BLASTOMYCOSIS (GILCHRIST'S DISEASE)

North American blastomycosis, caused by *Blastomyces dermatitidis*, is characterized by granulomatous and suppurative lesions which may occur in any organ of the body but are found most commonly in the skin, the lungs and the bones Two clinical forms can be differentiated, a primary cutaneous and a systemic form In the benign primary cutaneous form, one observes either one or a few rather large lesions In the fatal systemic form, the cutaneous lesions are numerous and usually small in size

The cutaneous lesions consist in both forms of verrucous plaques *showing an active border beset with a large number of minute abscesses* In the primary cutaneous form, the older lesions show central *healing with atrophy In the systemic form* the cutaneous lesions may undergo ulceration and, in addition, subcutaneous abscesses may occur

Histopathology. Histologic examination shows acanthosis, papillomatosis and considerable downward proliferation of the epidermis The downward proliferation may be marked enough to present the picture of pseudo epitheliomatous hyperplasia Intra-epidermal abscesses are often present Occasionally, one finds Langhans giant cells completely enclosed by the proliferated epidermis (Fig 106)

The dermis is infiltrated by a polymorphous granulation tissue Polymorphonuclear leukocytes usually are present in large numbers and form small abscesses in the dermis Langhans giant cells are scattered throughout the dermis They usually lie alone and not within *groups of epithelioid cells Occasionally, one observes* tuberculoid formations but never true tubercles

The cells, or spores, of *Blastomyces dermatitidis* are fairly numerous in histologic sections They are often found lying free in the tissue, *particularly in the abscesses* They occur, however, in their largest number within the giant cells One or several spores may lie within a giant cell (Fig 107) When in this location, the spores are easily spotted, even at low magnification, in sections stained with routine stains Being unstained, they resemble small, round holes punched out of the cytoplasm of the giant cells On high magnification, the spores are seen to have a thick wall, which gives them a double contoured appearance They measure from 8 to 15 microns in diameter, on the average 10 microns Blastomyces reproduce by



Fig 107 North American blastomycosis High magnification of Figure 106 Three blastomyces cells (B C) are shown lying in the cytoplasm of giant cells (X400)

budding, and occasionally budding forms are seen in sections Like in most fungus infections, many more spores are seen in sections stained with the Hotchkiss McManus stain than in routinely stained sections (see page 218)

The histologic appearance of the visceral lesions is analogous to that of the cutaneous lesions The number of neutrophils is often great and numerous abscesses tend to be present (Littman, Wicker and Warren)

Differential Diagnosis. Tuberculosis verrucosa cutis, torulosis and chromoblastomycosis must be considered in the differential diagnosis Tuberculosis verrucosa cutis shows no spores in the tissue In addition, the number of neutrophils is much smaller and one usually finds true tubercles and areas of caseation necrosis The distinctive features of torulosis and chromoblastomycosis are discussed under these respective headings (see below)

TORULOSIS (CRYPTOCOCCOSIS, EUROPEAN BLASTOMYCOSIS OF BUSSE AND BUSCHKE)

Torulosis, though very rare, occurs throughout the world The disease, caused by *Cryptococcus neoformans* (*Torula histolytica*), usually is chronic and systemic and ends in death The brain and the meninges are nearly always affected, resulting in meningo encephalitis with presence of the organisms in the spinal fluid The lungs also are commonly involved Cutaneous lesions are present in about 10 per cent of the cases, and, in rare instances, lesions of the oral mucosa occur (Cawley) The cutaneous lesions may be the first clinical sign of the disease (Linell, Magnusson and Norden), and in some instances the disease may remain limited to the skin (Gandy) In that case, the course of the disease is benign and self limited

The occurrence of torulosis has been reported either as a silent or as an active infection in patients with various types of lymphoma such as Hodgkin s disease (Geudel, Ende and Norman) and various types of leukemia (Cawley) A similar association with lymphoma occurs also in histoplasmosis (see page 231)

The cutaneous lesions are variable and may consist of papules, pustules, nodules, infiltrated plaques, ulcers or subcutaneous abscesses

Histopathology. Histologic examination of the skin shows, in most instances, a chronic inflammatory infiltrate with or without giant cells Occasionally, the inflammatory reaction is mild and extensive caseation is present in the dermis

The causative fungus usually is present in abundance, either within

giant cells or lying free in the tissue It consists of a spherical spore measuring from 5 to 10 microns in diameter which multiplies like *Blastomyces dermatitidis* by budding It usually is surrounded by a wide gelatinous capsule which does not stain with hematoxylin and [illegible] stains red with the periodic acid Schiff reaction and meta [illegible] (Linell Mag [illegible] sule is absent (Wile) The fungus then greatly resembles [illegible] *es dermatitidis* and easily can be confused with it especially since both may occur in giant cells On cultures however in contrast with *Blastomyces* *Torula* forms no mycelia (Benham)

CHROMOBLASTOMYCOSIS

This disease is limited to the skin and is benign It is caused by three closely related fungi which appear alike in the tissue *Hormo*

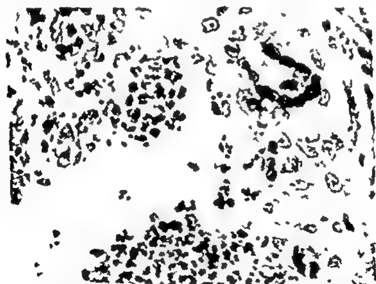


Fig 108 Chromoblastomycosis Periodic acid Schiff stain Epithelioid cells and Langhans giant cells form the wall of an abscess Two long chains of fungus cells are located in the right upper corner In addition three fungus cells lie in the right center (X400)

dendrum pedrosoi Phialophora verrucosa and *Hormodendrum compactum* (French and Russell)

The cutaneous lesions usually limited to a single area consist of densely aggregated nodules and plaques with a hard verrucous surface

Histopathology. The histologic appearance of the skin is very much like that of blastomycosis The epidermis shows considerable hyperplasia although rarely to the extent that is usual in blastomycosis The dermis shows an intensive infiltration, with a polymorphous granulation tissue containing many Langhans giant cells and small abscesses composed of polymorphonuclear leukocytes Tuberculoid formations may be present, but true tubercles and caseation are absent, just as in blastomycosis

The causative organisms are found in Langhans giant cells as well as free in the tissue and are especially numerous in the abscesses They appear as sclerotic, dark brown, thick-walled, usually spherical spores varying in size from 8 to 15 microns They lie either singly or in chains or clusters (Fig 108) Reproduction is by intracellular wall formation and splitting not by budding In some of the organisms cross walls can be seen

Differential Diagnosis. Chromoblastomycosis cannot be differentiated from blastomycosis except through the different appearance of the fungi Just as blastomycosis chromoblastomycosis differs from tuberculosis verrucosa cutis by the presence of a fungus in the tissue, and the absence of true tubercles and of caseation

COCCIDIOIDOMYCOSIS (SAN JOAQUIN VALLEY FEVER)

Coccidioidomycosis is caused by *Coccidioides immitis* It is endemic in the southwestern United States especially in the San Joaquin valley of California and in northern Mexico Three forms are recognized, primary, intermediate and progressive (Duemling)

Primary coccidioidomycosis represents an acute respiratory infection Development of erythema nodosum is not uncommon

Progressive coccidioidomycosis (coccidioidal granuloma) follows the primary form in a small percentage of cases after a varying length of time It has a very high mortality Many organs especially the meninges, the lungs the bones and the lymph nodes may be involved Cutaneous lesions are common They consist either of verrucous and granulomatous nodules or of subcutaneous cold abscesses which may break through the skin

Histopathology. *The nodose lesions of primary coccidioidomycosis* have the same histologic appearance as idiopathic erythema nodosum (Winer)

The verrucous and the granulomatous lesions of coccidioidal granuloma resemble blastomycosis in their histologic aspects How

ever there is less tendency to abscess formation, and caseation necrosis may occur (Moore) The causative organisms are found free in the tissue as well as in Langhans giant cells As a rule they are present in large number

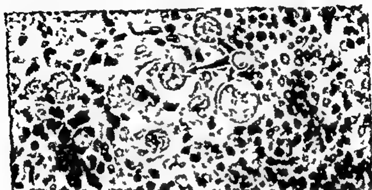


Fig 109 Coccidic
larger than those o
size Their cytoplas

The subcutaneous abscesses of coccidioidal granuloma resemble scrofuloderma in their l ocalog n m on n C

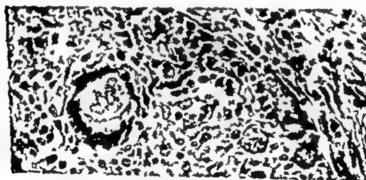


Fig 110 Coccidioidomycosis A large *Coccidioides* spore lies within a giant cell The *Coccidioides* spore contains numerous endospores (×400)

theloid cells and some giant cells Numerous spores are present extracellularly as well as intracellularly in giant cells

The spores of C
60 microns 10 to
Thus

Coccidioides is much larger than *Blastomyces, Torula* or *Phialophora*. The spores are spherical and thick walled and have a granular cytoplasm. Multiplication is not by budding but by formation of endospores which may be seen lying inside the larger spores (Fig 110). The endospores are released into the tissue by rupture of the wall of the spore. Endospores may measure up to 5 microns in diameter.

Differential Diagnosis. A diagnosis of coccidioidomycosis can be made only in the presence of the fungus.

ACTINOMYCOSIS

Actinomycosis is caused either by *Actinomyces bovis*, which is anaerobic or micro aerophilic, or by several species of *Nocardia* (e g *N asteroides, N madurae*), which are aerobic.

Actinomycosis frequently affects the skin. Involvement may be primary, as in Madura foot (mycetoma). More often, however, the infection reaches the skin from an internal focus. The most common form is cervicofacial actinomycosis, in which case the organism reaches the skin from the mouth, next in frequency are actinomycosis of the thoracic skin secondary to involvement of a lung and actinomycosis of the abdominal skin secondary to involvement of the cecum or the appendix.

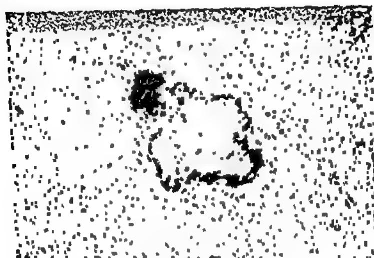
The involved skin is dark red in color, possesses a "wooden" type of hardness and shows numerous sinuses discharging a serosanguineous or purulent fluid containing sulfur yellow granules which consist of masses of fungi.

Histopathology. Histologic examination shows extensive granulation tissue containing large abscesses. The fungus granules are found within the abscesses. The granulation tissue is nonspecific in its appearance. In the early phase of the disease it is composed of neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes and fibroblasts. In the healing phase fibroblasts predominate. Thus, the diagnosis can be established only by finding the *Actinomyces* granules in the abscesses. When selecting an area for biopsy, an area containing purulent material should be chosen.

The fungus granules are large and may measure several hundred microns in diameter, large enough to be visible macroscopically as the so called sulfur granules. In histologic sections, they appear baso[illegible] (Fig 111). They are homogeneous [illegible] branching filaments at the periphery. The ends of the filaments frequently are surrounded by a gelatinous sheath, giving the ends a club shaped appearance. The filaments are much better seen in sections stained by Gram's method, which stains them Gram positive, than in sections stained with routine stains. The

cells immediately around the granules are usually polymorphonuclear leukocytes, but foreign body giant cells occasionally are seen in contact with the granules

In general, *Nocardia* produces more necrosis and less granulation tissue and less fibrosis than *Actinomyces* The granules of *Nocardia* are smaller and much less numerous than those of *Actinomyces* so that multiple sections are necessary to find them (Weed and Baggen



...tinomycosis A large "sulfur granule" is shown in the center of the field The granule appears homogeneous in the center Clubs are present at the periphery (×100)

stoss) Nevertheless, these differences are not sufficiently distinct and cultural studies are necessary for a differentiation of *Nocardia* from *Actinomyces*

SPOROTRICHOSIS

Spor... nckii, affects only the ... benign disease Most ... localized type of infection In that type there is a primary lesion (sporotrichotic chancre) which is commonly an ulcer but may be papillomatous Secondarily, multiple subcutaneous nodules appear along the lymphatics dr... area The nodules ...

Much ... the dis seminate... ...that are widely scattered lesions consisting of ... the localized type, form

Coccidioides is much larger than *Blastomyces, Torula* or *Phialophora*. The spores are spherical and thick walled and have a granular cytoplasm. Multiplication is not by budding but by formation of endospores which may be seen lying inside the larger spores (Fig. 110). The endospores are released into the tissue by rupture of the wall of the spore. Endospores may measure up to 5 microns in diameter.

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The involved skin is dark red in color, possesses a wooden type of hardness and shows numerous sinuses discharging a serosanguineous or purulent fluid containing sulfur yellow granules which consist of masses of fungi.

Histopathology. *Histologic examination shows* extensive granulation tissue containing large abscesses. The fungus granules are found within the abscesses. The granulation tissue is nonspecific in its appearance. In the early phase of the disease it is composed of neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes and fibroblasts. *In the healing phase fibroblasts predominate.* Thus the diagnosis can be established only by finding the *Actinomyces* granules in the abscesses. When selecting an area for biopsy, an area containing purulent material should be chosen.

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thick walled round spores are found free in the tissue visible even with hematoxylin eosin staining Some of them have radiating asteroid elongations (Fig 112) (Moore and Ackerman Pinkus and Grekin)

Differential Diagnosis Without the demonstration of the fungus a diagnosis of sporotrichosis cannot be made but can only be suspected The subcutaneous nodules of tularemia may have the same histologic appearance Erythema induratum differs from sporotrichosis by its vascular changes and the *presence of caseation* which is absent in sporotrichosis

HISTOPLASMOSIS

Histoplasmosis caused by the fungus *Histoplasma capsulatum* in most instances is a fatal systemic disease Occasionally the disease is limited to the skin or the mucous membranes and benign in its course (Curtis and Grekin)

In the systemic form of histoplasmosis the clinical *picture is* variable The lymph nodes are often enlarged markedly Pulmonary and adrenal involvement may be a *prominent feature Cutaneous* or *mucomembranous* lesions occur in about half the patients with the systemic form of *infection* (Miller Keddie Johnstone and *Bostick*

Several authors have reported the simultaneous occurrence of [illegible] sease (Ende [illegible] and Curtis) [illegible] to the lymphoma especially in view of the fact that also torulosis has been observed in *association* with lymphoma (see page 224)

The skin lesions of histoplasmosis in both the systemic and the cutaneous form may be *nodular* granulomatous or ulcerative

Histopathology *Histologic* examination reveals a chronic nonspecific granulomatous *infiltrate with foci of necrosis* Throughout this infiltrate but *especially in the vicinity of the* necrotic foci one observes large *histiocytes (macrophages)* engorged with numerous organisms

Histoplasma capsulatum appears in sect[illegible]ned with hema [illegible] surrounded by [illegible] organism meas[illegible] *microns in diameter* On staining with the *periodic* acid Schiff *reaction* however *Histoplasma capsulatum* shows no capsule but instead the body appears larger and lined by a definite red stained cell wall *Therefore* it appears that the so-called halo or

Histopathology. The primary lesion of sporotrichosis shows a non specific granulation tissue containing, among other cells, many plasma cells, epithelioid cells and some Langhans giant cells Foci of suppuration are present If the primary lesion is papillomatous, one finds, in addition, marked epithelial hyperplasia and intra epi dermal abscesses (Moore and Ackerman)

The subcutaneous nodules show a more characteristic appearance than the primary lesion because of the arrangement of the infiltrate



FIG 112 Sporotrichosis A large spore with radiating "asteroid" elonga tions is shown (×1350) (Hermann Pinkus M D)

in three zones—the chronic suppurative zone, the tuberculoid zone and the syphiloid zone The zone in the center of the nodule, the *chronic suppurative zone* is composed chiefly of neutrophils with a few histiocytes and lymphocytes Small abscesses composed entirely of neutrophils are present within this zone The middle or tubercu loid zone is characterized by numerous epithelioid cells and a large number of giant cells of the Langhans type The giant cells may lie *in groups* The peripheral or syphiloid zone consists of a richly cel lular infiltrate of plasma cells, lymphocytes and fibroblasts The zonal arrangement is not always distinct In older nodules one merely sees a nonspecific granuloma

The causative organisms are present in the tissue in small numbers as round to fusiform bodies which do not stain with hematoxylin and eosin but become visible when the periodic acid Schiff reagent is employed (Kligman and Baldridge) In rare instances a few large,

Torulosis

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1a (Good review)
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capsule is an artefact produced by plasmolysis which causes the cytoplasm to shrink away from the cell wall (Kligman and Baldridge) *Histoplasma capsulatum* is a fungus according to its cultural characteristics and because it multiplies by budding

Differential Diagnosis The general appearance of the granulomatous infiltrate with its parasitized histiocytes is much like that of rhinoscleroma, granuloma inguinale and cutaneous leishmaniasis (For their differential diagnosis see Table 5 page 237)

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epidermis grafted on the chorio allantois of chick embryos with the fluid obtained from herpes zoster vesicles

It is probable that the viruses of varicella and herpes zoster are identical There exists strong clinical evidence (Brunsgaard) and experimental evidence (Brain) for this contention Furthermore the two viruses have an identical appearance under the electron microscope (Baldridge Blank and Rake) Wise and Sulzberger believe that herpes zoster represents an immune or allergic form of varicella which occurs in patients who had previous clinical or subclinical varicella

Clinical Appearance Variola shows a generalized eruption which at first consists of papules After two or three days the papules are transformed into vesicles which are characteristically umbilicated After three more days the vesicles change into pustules In severe cases in addition there may be purpuric lesions It is characteristic of variola that all lesions are at the same stage of development

The eruption of varicella is also generalized The lesions begin as small papules which soon develop into vesicles The vesicles crust over as a rule without changing into pustules Lesions occur in successive crops so that one observes lesions in different stages of development

b

t

loca ized eruption there is a generalized vesicular eruption indistinguishable from that of varicella Herpes zoster (especially the generalized form) is apt to occur in lymphoma (see page 491)

Herpes simplex shows one or several groups of vesicles on a mildly inflammatory base The eruption may occur anywhere on the skin but is found most commonly about the face and the genitalia

Histopathology The characteristic histologic lesion in the four diseases is an intra epidermal vesicle produced by profound degeneration of epidermal cells Because of the presence of these degenerative changes the vesicle differs histologically from those seen in other

n of Bullae page 66) and

er it is important that as

ion be selected for biopsy

invasion of inflammatory

cells—may obscure the diagnostic features The degeneration of the epidermal cells occurs in two forms ballooning degeneration and reticular degeneration

Ballooning de-

cells Such

eosinophilic cytoplasm (Figs. 114, 115). They may have no nucleus, or may have one or many. Because of the fact that the balloon cells lose their intercellular bridges, acantholysis occurs and the cells become separated from one another. Unilocular vesicles result. The process of ballooning degeneration occurs mainly at the base of virus vesicles leading to a dissolution of the lower epidermis, so that, ulti



FIG 114 Herpes zoster. Low magnification There is marked ballooning degeneration of the cells at the floor of the vesicle The cells of a hair follicle, shown at the left, likewise show ballooning degeneration Reticular degeneration observed at the top of the vesicle, is only slight Since this is an early lesion, no inflammatory reaction is present (×100)

mately, the originally intra epidermal vesicles become subepidermal in many places Ballooning degeneration affects also the epithelial cells of hair follicles and sebaceous glands

Reticular

cells become

the cell wall bursts By coalescence of neighboring, similarly affect… cells, a multilocular vesicle results, the septa of which are formed by the resistant cellular walls (Fig 116) Reticular degeneration occurs mainly at the top and the periphery of virus vesicles In older vesicles, the resistant cellular walls disappear and the multilocular vesicle then becomes unilocular *It may be pointed out that reticular* degeneration is not specific for virus vesicles since it also occurs in the vesicles of dermatitis (see page 68).

numerous polymorphonuclear leukocytes as well as some macrophages (Sheldon and Heyman) These central abscesses tend to have a triangular or quadrangular shape with elongated corners, giving them a stellate appearance (Fig 124) The epithelioid cells surrounding the abscesses are arranged in palisade formation As the abscesses gradually enlarge, they coalesce and lose their stellate appearance

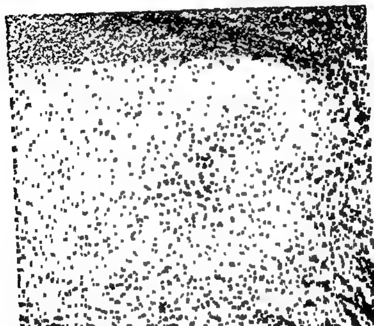


Fig 124 Lymphogranuloma venereum In the lymph node, a stellate abscess is present It is surrounded by epithelioid cells in palisade formation (×100)

MILKERS' NODULES

Milkers nodules are acquired from cows infected with paravaccinia (natural cowpox) There are, usually on the fingers, one to three and occasionally more nodules, 1 to 2 cm in diameter, which are bluish red, semiglobular and usually painless Spontaneous healing occurs in 1 to 2 months

Histopathology The epidermis shows acanthosis and parakeratosis. A dense nonspecific chronic inflammatory infiltrate is present in the dermis The capillaries are increased in number, are dilated and show swelling of their endothelial cells (Nomland and McKee)

While most authors have found no inclusion bodies, Katzenellenbogen observed them in some but not in all of his cases They were

located in the cytoplasm of vacuolated epidermal cells and often were Feulgen positive Their appearance was similar to that of the inclusion bodies observed in variola and vaccinia

Study of smears of tissue obtained from milkers nodules under the electron microscope has shown the presence of typical elementary bodies of the paravaccinia type (*Nasemann and Deubner*)

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located in the cytoplasm of vacuolated epidermal cells and often were Feulgen positive Their appearance was similar to that of the inclusion bodies observed in variola and vaccinia

Study of smears of tissue obtained from milkers nodules under the electron microscope has shown the presence of typical elementary bodies of the paravaccinia type (Nasemann and Deubner)

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Variola Varicella Herpes Zoster Herpes Simplex

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16

Metabolic Diseases

LIPOIDOSES

The term lipoidoses has been applied to a group of diseases in which the lesions, due to a local or generalized disturbance of the lipid metabolism, contain lipid substances.

No generally accepted classification of the lipoidoses exists The following classification is based largely on the classifications published by Thannhauser and by Montgomery and Osterberg

I Lipoidoses with Increased Blood Lipids
  1 Primary hypercholesteremic xanthomatosis
  2 Biliary xanthomatosis
  3 Idiopathic hyperlipemia
  4 Secondary hyperlipemia
II Lipoidoses with Normal Blood Lipids
  5 Lipid reticulo-endotheliosis (Hand Schuller Christian disease)
    a Fulminating type Letterer Siwe disease
    b [illegible]

  [illegible]

  8 Lipoid proteinosis
  9 Extracellular cholesterosis
III Localized Lipoidoses
  10 Xanthelasma palpebrarum
  11 Necrobiosis lipoidica

Lipoidoses with Increased Blood Lipids

1 *Primary Hypercholesteremic Xanthomatosis*

Primary [illegible] neutral fat Therefore the serum is clear.

Cutaneous lesions consist of flat or slightly raised xanthelasmata on the eyelids and tuberous xanthomata, especially on the elbows and the knees In addition, there are tendon xanthomata, especially on the Achilles tendons, the patellar tendons, and the extensor ten

Sheldon W H and Heyman A Lymphogranuloma venereum Am J Path. 23 653 1947

Milkers Nodules

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in xanthoma cells to be anisotropic (doubly refractile) in contrast with the fat in the sebaceous cells and the subcutaneous fat cells, which is isotropic (not doubly refractile) (See page 31)

Xanthoma cells form from perithelial cells, which are histiocytes They have usually one nucleus but may have two and even many



Fig 126 Xanthoma tuberosum early lesion Scarlet red stain for fat The xanthoma cells are filled with lipid material (×100)

nuclei In multinucleated xanthoma cells the nuclei either are irregularly distributed as in *foreign body giant cells*, or lie near the center of the cell grouped around a small island of nonfoamy cytoplasm and surrounded by foamy cytoplasm This latter [illegible]

[illegible] an admixture of inflammatory cells, particularly polymorphonuclear leukocytes, lymphocytes and histiocytes In well-developed lesions the infiltrate is composed almost entirely of xanthoma cells (Fig 125) Fat stains in this stage show

dons of the hands Atherosclerotic cardiovascular disease is common and may lead to death due to coronary occlusion in early life (Bloom Kaufman and Stevens)

Histopathology. The histologic appearance of the cutaneous and the tendinous lesions is characterized by the presence of xanthoma or foam cells Xanthoma cells are phagocytic cells filled with lipid drop



FIG 125 Xanthoma tuberosum, early lesion Numerous xanthoma cells (foam cells) are present There is only little fibrosis (×200)

lets In routine sections, the lipid droplets have been dissolved and extracted in the process of fixation and embedding so that the cells have a reticulated or foamy appearance (Fig 125) However, the lipid droplets can be seen when formalin fixed frozen sections are stained with fat stains, such as scarlet red (Fig 126) With scarlet red, the lipid substance in the xanthoma cell stains a brownish red, in contrast to the lipid substance in sebaceous glands and the subcutaneous fat, which stains a bright orange red This is due to the fact that the lipid substance in xanthoma cells is predominantly cholesterol and phospholipids, whereas the lipid substance in the sebaceous cells and the subcutaneous fat cells is predominantly neutral fat Polariscopic examination of frozen sections reveals the lipid droplets

xanthomatous lesions often by many years The blood serum is clear but due to its high content of bilirubin it is intensely green

The biliary cirrhosis which causes the xanthomatous lesions is produced as a rule either by cholangiolitis or by extrahepatic obstruction (MacMahon) but occasionally in children by congenital hypoplasia of bile ducts (MacMahon and Thannhauser)

Histopathology The cutaneous lesions show the same histologic picture as is found in primary xanthomatosis

3 *Idiopathic Hyperlipemia*

In idiopathic hyperlipemia which usually is not familial the blood serum shows an elevation not only of the cholesterol and phospholipids as in primary hypercholesteremic xanthomatosis but also of the neutral fat Therefore the blood serum is milky

The cutaneous lesions are of two types tuberous xanthomata which are found especially on the elbows and the knees and papular xanthomata which may be diffusely distributed but are most prevalent on the buttocks The papular xanthomata have a tendency to come and go and therefore are often referred to as eruptive xanthomata Xanthelasmata of the eyelids are absent but tendon xanthomata may occur (Lever Smith and Hurley)

Visceral manifestations occasionally are present They include hepatosplenomegaly attacks of abdominal pain due to secondary pancreatitis and coronary heart disease which however *occurs less* frequently than in primary hypercholesteremic xanthomatosis The association of idiopathic hyperlipemia with hepatosplenomegaly occasionally is referred to as Burger Grutz disease

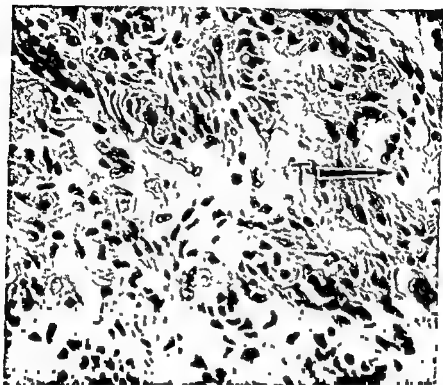
Histopathology The histologic appearance of the xanthomata in idiopathic hyperlipemia is the same as that of the *xanthomata in* primary hypercholesteremic xanthomatosis The papular xanthomata which usually are of recent origin often show like most young xanthomata an admixture of inflammatory cells *(see page 259)*

Only few reports on the histology of the visceral lesions are available In one patient with hepatosplenomegaly conspicuous fat infiltration of the liver cells was observed on biopsy (Movitt Gerstl Sherwood and Epstein) The presence of pancreatitis in patients with attacks of abdominal pain has been confirmed repeatedly by exploratory operation (Klatskin and Gordon)

4 *Secondary Hyperlipemia*

Secondary hyperlipemia may occur secondary to severe diabetes (xanthoma diabeticorum) to *nephrosis* and to glycogen storage disease (von Gierke s disease) The amounts of cholesterol phospho

that all fat is intracellular In involuting lesions, fibroblasts appear (Fig 127) Ultimately, fibrosis replaces the foam cells Weidman and Schaffer express the belief that the foam cells themselves can become transformed into fibroblasts In old fibrosing lesions cholesterol may be found not only in foam cells but also extracellularly



center of the cell grouped around a small island of nonfoamy cytoplasm and surrounded by foamy cytoplasm (×400)

Differential Diagnosis. Differentiation between a fibrotic lesion of *xanthoma tuberosum* and histiocytoma may be very difficult and even impossible It may be necessary to rely upon clinical and blood chemical data for the correct diagnosis (Montgomery and Osterberg)

2 *Biliary Xanthomatosis*

Biliary cirrhosis may cause high values for cholesterol and phospholipids in the serum and lead to xanthelasmata on the eyelids and tuberous xanthomata on the skin that are indistinguishable from those of primary hypercholesteremic xanthomatosis However, deep jaundice is *present* and the jaundice precedes the appearance of

xanthomatous lesions often by many years The blood serum is clear but due to its high content of bilirubin it is intensely green

The biliary cirrhosis which causes the xanthomatous lesions is produced as a rule either by cholangiolitis or by extrahepatic obstruction (MacMahon) but occasionally in children by congenital hypoplasia of bile ducts (MacMahon and Thannhauser)

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Visceral manifestations occasionally are present They include hepatosplenomegaly attacks of abdominal pain due to secondary pancreatitis and coronary heart disease which however occurs less frequently [illegible] The association [illegible] occasionally [illegible]

Histopathology The histologic appearance of the xanthomata in [illegible] at of the xanthomata in [illegible] The papular xanthomata [illegible] show like most young xanthomata an admixture of inflammatory cells (see page 259)

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4 Secondary Hyperlipemia

Secondary hyperlipemia may occur secondary to severe diabetes (xanthoma diabeticorum) to nephrosis and to glycogen storage disease (von Gierke s disease) The amounts of cholesterol phospho-

lipids and neutral fat in the serum are elevated and the serum is milky.

Papular eruptive xanthomata occur which usually are diffusely distributed but have a predilection for the buttocks. Occasionally, recently erupted papules have an inflammatory base.

Histopathology. The papular xanthomata of secondary hyperlipemia show the same histologic picture as other xanthomata. Since they usually are of recent origin, a rather marked inflammatory infiltrate may be present with large numbers of neutrophils. In the involuting stage, much of the cholesterol may be seen in phagocytes and extracellularly (Montgomery and Osterberg).

Lipoidoses with Normal Blood Lipids

5. *Lipid Reticulo-endotheliosis (Hand-Schuller-Christian Disease)*

Letterer-Siwe disease, Hand-Schuller-Christian disease and eosinophilic granuloma represent variations in degree, stages of development and localization of the same basic disease process (Farber). Formerly, Hand-Schuller-Christian disease was regarded as a primary disturbance of the lipid metabolism, as a normocholesteremic xanthomatosis (Thannhauser and Magendantz), but this concept has been abandoned (Mallory) and the presence of cholesterol in the lesions is now regarded as a secondary infiltration. The three diseases are at present believed to be histiocytoses or reticulo-endothelioses. If the reticulo-endotheliosis occurs in infancy, it is generalized and rapidly fatal (*Letterer-Siwe disease*), death occurs before sufficient time has elapsed for the development of the lesion into a lipogranuloma. In early childhood, the disease is chronic (Hand-Schuller-Christian disease), and lipidization is as a rule pronounced. In later childhood or in the adult the usual picture is that of eosinophilic granuloma which represents an abortive form of the disease. Transitional cases between these three forms of reticulo-endotheliosis are common. The values for blood plasma lipids are normal in all three forms.

Letterer-Siwe Disease (Nonlipid Histiocytosis of Foot and Olcott). This disorder usually occurs in infants and is almost inevitably fatal within a few months. It is characterized by fever, anemia, enlargement of the liver and the spleen, lymphadenopathy and multiple defects of the bones. In most cases cutaneous lesions are present. They may consist of petechiae, papules or pustules. In some cases one observes numerous closely set, brownish papules covered with scales or crusts. This type of eruption usually is extensive with a predilection *to involve the scalp, the face* and the trunk.

The resemblance of the eruption to seborrheic dermatitis and Darier's disease is often striking (Laymon and Sevenants)

Histopathology The cutaneous lesions show usually close to the epidermis and often invading into the epidermis (Fig 128) accumulations of histiocytes (reticulum cells) intermingled with a few lymphocytes and varying numbers of eosinophils Extravasated blood cells frequently lie in and about the masses of histiocytes The histiocytes appear as large cells with irregularly shaped vesicular nuclei and abundant slightly eosinophilic cytoplasm (Fig 129) In some areas these cells are distinctly outlined and even separated by edema but in other areas their cytoplasm is confluent Occasionally some of the cells have a foamy cytoplasm and stain positive for fat with fat stains The epidermis may become destroyed by pressure of the underlying cells (Foot and Olcott Abt and Denenholz Lane and Smith case I)

The visceral lesions consist of proliferations of large pale reticulo endothelial cells which invade and replace the normal structure of spleen liver bone marrow lymph nodes and other organs (Sweitzer and Laymon)

Hand Schuller Christian Disease Diabetes insipidus exophthalmos and multiple defects of the bones especially of the cranium represent the triad of typical Hand Schuller Christian disease However any one or even all three of the cardinal symptoms may be absent and involvement may occur in entirely different organs For example enlargement of the liver the spleen and the lymph nodes is common and dwarfism is observed occasionally Hand Schuller Christian disease takes a chronic course usually extending over years and has a mortality of about 70 per cent

Cutaneous lesions are quite uncommon If present they are similar to those seen in Letterer Siwe disease consisting of an extensive eruption of coalescing scaly or crusted papules with a distinct clinical resemblance to Darier's disease Occasionally the term xanthoma disseminatum is used for this eruption

Histopathology Early cutaneous lesions of Hand Schuller Christian disease show the same histologic picture as the cutaneous lesions of Letterer Siwe disease (Lane and Smith Laymon and Sevenants) In mature lesions a large number of the histiocytes show a foamy cytoplasm and typical foam cells may be present (Thannhauser and Magendantz) In old lesions the number of foam cells again may be small and foreign body giant cells may be found As a rule the tendency to lipidization is less pronounced in the cutaneous lesions than in the lesions of other organs



FIG 128 Hand Schuller Christian disease (eosinophilic granuloma) Low magnification The upper portion of the dermis contains an infiltrate composed almost entirely of loosely aggregated histiocytes The infiltrate has invaded the epidermis in many areas (×100)

FIG 129 I ... loma) High magnificatic ... shaped nuclei and abundant ... invaded the epidermis (×400)

Eosinophil

ease of this gr

They occur

involved The cutaneous lesions consist either of an extensive eruption of crusted papules as in Letterer Siwe and Hand Schuller Christian disease (Lever and Leeper) or of one or several erythematous granulomatous plaques which may undergo ulceration (Curtis and Cawley McCreary) The two types of lesions may be present simultaneously (Granuloma faciale formerly called eosinophilic granuloma of the face is an entirely different disease from eosinophilic granuloma and is not related to it For its description see page 111)

Histopathology The papules have the same histologic appearance as in Letterer Siwe disease namely an infiltrate of loosely aggregated large

is and invading the epi

The number of eosino

The granulomatous plaques also show numerous loosely arranged large histiocytes within an edematous stroma Eosinophils are present in varying numbers They usually lie in patches rather than diffusely distributed through the lesion In addition a few lymphocytes and plasma cells are present (Curtis and Cawley McCreary Lever and Leeper)

Lipid is absent in the cutaneous lesions but may be present in the associated osseous lesions

6 *Niemann Pick Disease*

Niemann Pick disease is characterized by abnormal deposits of sphingomyelin a diaminophosphatide in the reticulo endothelial cells of many organs but not in the skin The level of lipids in the blood serum is normal

The disease occurs as a rule in Jewish infants and is fatal There are enlargement of the liver and the spleen cachexia and brownish discoloration of the skin

Histopathology On histologic examination the brownish discoloration of the skin is found to be due to the presence of increased amounts of melanin

7 *Gaucher s Disease*

In Gaucher s disease kerasin a cerebroside is deposited in the reticulo endothelial cells of many organs The skin however is spared The blood lipids are normal

The disease tends to be familial, occurs predominantly in Jews may start at any age and takes a chronic course There is hepatosple

nomegaly and rarefaction with cortical thickening of the long bones The skin shows brownish discoloration

Histopathology The skin shows increased amounts of melanin

9 *Lipoid Proteinosis (Urbach Wiethe)*

Lipoid proteinosis is characterized by lipid infiltrations of the skin of the oral mucosa and of the larynx Although the blood lipids may



Fig 150 Lipoid proteinosis The dermis is occupied by thick wavy hyalin like bundles which run perpendicular to the epidermis In addition the hyalin like material surrounds all blood vessels as a thick mantle (×200)

be normal (Wise and Rein Price LaRosa and Settle) there may be an increase in the total lipids (Hansen Ramos e Silva) or a relative increase in phospholipids (Montgomery and Havens Wile and Snow) The disease is often familial

Clinically, one observes nodular and verrucous lesions on the skin and on the mucous membranes of the mouth and the larynx The nodules of the skin on regressing leave pitted scars giving the skin a

l there is hoarse-

ı is striking and
ırregular acan



Lipoid proteinosis Scarlet red stain for fat. A large amount of lipid material is present. It occurs in the form of small droplets throughout the hyaline material, particularly around the blood vessels (×100)

thosis The dermis is considerably thickened The upper half of the dermis is occupied by thick, wavy bundles which are

the nuclei of
dermis and of the vascular endothelium are well preserved In the lower dermis, the collagen appears normal but the

homogeneous material is present around some of the vessels and sweat glands

On staining with scarlet red, a large amount of lipid material is visualized It stains a rusty brown and occurs in the form of small droplets throughout the hyalin like material, but particularly around the blood vessels (Fig 131) It is located extracellularly On polariscopic examination, the lipid material proves to be isotropic, not doubly refractile Urbach and Wiethe interpreted the histologic findings as indicating a merging of lipid and protein and, therefore, suggested the name lipoid proteinosis

No definite conclusion has so far been reached about the nature of the lipid substance in the dermis In several cases, the chemical analysis of involved skin revealed a decided increase in the amount of lecithin, which is a monoaminophosphatide (Montgomery and Havens Ramos e Silva) In other cases, however, no such increase was found (Wile and Snow, Hansen, Price, LaRosa and Settle)

9 *Extracellular Cholesterosis (Urbach)*

This disorder is characterized by extracellular cholesterol infiltrations in the skin

Only three cases of this condition have been reported in the literature (Urbach, Epstein and Lorenz Laymon Sobel and Pollock) All three cases showed reddish brown verrucous plaques and nodules involving especially the dorsa of the hands and the feet and the extensor surfaces of the legs Ulceration of some of the lesions occurred in Sobel s case The amount of cholesterol in the blood serum was normal in Laymon s case and subnormal in Urbach s and Sobel s cases

Histopathology. The involved skin shows a dense, nonspecific cellular infiltrate composed mainly of histiocytes and lymphocytes The blood vessels are dilated and their endothelium is swollen No foam cells are present In healing lesions there is considerable fibrosis

Fat stains reveal numerous droplets of fat in extracellular position throughout the lesions but especially about the blood vessels On polariscopic examination the fat droplets are doubly refractile

Chemical examination of tissue in Urbach s and Sobel s cases revealed the content of cholesterol three to five times greater in the lesions than in the normal skin

The cause of the disease is unknown Sobel and Pollock impressed with the subnormal values for cholesterol in their as well as in Urbach's case, suggest that, for some unknown reason, the blood is unable to hold normal amounts of cholesterol which, therefore, is

deposited in the tissue Being unable to metabolize the cholesterol the tissue responds not with foam cell formation but instead with a severe inflammatory reaction as if dealing with a foreign body of irritating or toxic nature

Localized Lipoidoses

10 Xanthelasma Palpebrarum

This disorder is characterized by the presence of soft yellowish plaques on the eyelids caused by the deposition of cholesterol Although xanthelasma palpebrarum is common in primary hyper cholesteremic xanthomatosis (see page 257) it frequently occurs in individuals with little or no elevation of the serum cholesterol (Epstein Rosenman and Gofman) Since in such instances the deposition of cholesterol probably is caused by local degenerative changes in the skin of the eyelids xanthelasma palpebrarum is best regarded as a localized lipoidosis

Histopathology The histologic changes are similar to those of primary xanthomatosis As a rule however fewer Touton cells are seen and they may be absent Fibrotic changes may occur (Montgomery and Osterberg)

11 Necrobiosis Lipoidica

This disease represents a localized lipoidosis inasmuch as the deposition of lipids occurs in areas in which degeneration or necrobiosis of collagen has taken place The necrobiosis of collagen is due to vascular changes (Roederer Woringer and Burgun) In those cases in which diabetes exists it can be assumed that the diabetes has caused the vascular changes However diabetes originally thought to be a prerequisite for this disease is present in only about one third of the cases (Kaalund Jørgensen) In the other two thirds the cause of the vascular changes is unknown

Clinically one observes on the legs and rarely elsewhere on the skin one or several sharply demarcated irregularly outlined glazed patches which are yellow in the center and violaceous at the periphery The center gradually becomes depressed and atrophic and may break down to form an ulcer

Histopathology On histologic examination the epiderm[illegible]

[illegible] especially in the lower portions In these areas the collagen appears homogeneous swollen and partly basophilic (Fig 132) The collagen bundles often are broken up and,

homogeneous material is present around some of the vessels and sweat glands

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degeneration In contrast with the neutral fat in the subcutaneous layer and the sebaceous glands, which stains a brilliant orange red, the granules stain a rusty brown According to Hildebrand, Mont ... phos ... terol ... ion

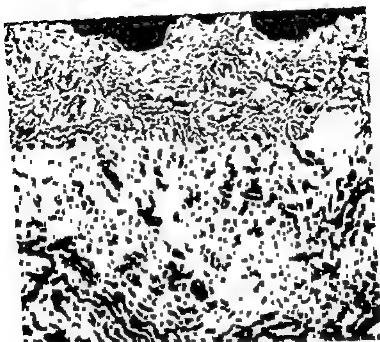


Fig 133 Necrobiosis lipoidica *Several foreign-body giant cells are located within an area of collagen degeneration Two fibrotic vessels are present (×200)*

(Laymon and Fisher) *The fact that* occasionally, lipids are absent in the lesions (Sachs) *indicates that* their presence is purely a secondary phenomenon

Granulomatosis *disciformis* chronica progressiva recently described by several European *authors* (Miescher and Leder, Arzt) probably *represents* necrobiosis lipoidica without lipid deposits

Differential Diagnosis. *In* the differential diagnosis, granuloma annulare must be considered, *because* both necrobiosis lipoidica and granuloma annulare *show* areas of collagen degeneration and the same type of reactive *inflammation* and fibrosis However in granuloma annulare there are no vascular changes no deposits of *lipids* few or no giant cells *and no* atrophy or ulceration of the epidermis,

instead of lying parallel to the surface of the skin extend in various directions There often is evidence of formation of young collagen between the degenerated bundles

Within and near the areas of necrobiosis often extending into the subcutaneous fat one finds a predominantly perivascular inflammatory infiltrate composed of lymphocytes histiocytes fibroblasts and

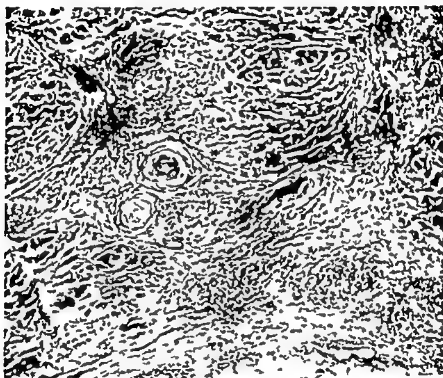


Fig 132 Necrobiosis lipoidica Much of the collagen appears degenerated An inflammatory infiltrate is scattered through the areas of degeneration A vessel in the center shows endothelial proliferation and fibrosis of its wall (×100)

occasional groups of epithelioid cells Foreign body giant cells commonly are present and thus are of considerable diagnostic value (Michelson and Laymon Belote and Welton) (Fig 133) Occasionally a few foam cells are noted (Klaber Nicholas)

The blood vessels particularly in the middle and the lower dermis exhibit fibrosis of their walls with proliferation of their endothelial lining This process may lead to partial and occasionally even to complete occlusion of the lumen Thrombosis of small vessels occurs sometimes These vascular changes account for the degeneration of the collagen

Staining for fat with scarlet red frequently but not always reveals numerous granules of lipid extracellularly in the areas of collagen



Fig 134 Primary systemic amyloidosis Round amorphous fissured masses of amyloid are present in the uppermost dermis. They resemble those of colloid milium but in contrast to colloid milium are present throughout the dermis (×200)

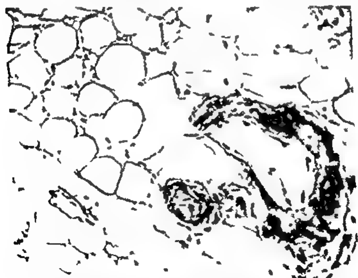


Fig 135 Primary systemic amyloidosis Subcutaneous fat. Amyloid is deposited *in the walls of two blood vessels* and also around fat cells forming so-called amyloid rings (×400)

on the other hand, deposits of mucin usually are present In spite of these differences, Ellis and Kirby Smith regard the two diseases as closely related

AMYLOIDOSIS

Three forms of amyloidosis exist (1) primary systemic amyloidosis (2) primary localized amyloidosis of the skin (lichenoid amyloidosis) and (3) secondary systemic amyloidosis In primary systemic amyloidosis, the skin is frequently involved, in secondary systemic amyloidosis, very rarely

The Congo red test is of great value in the diagnosis of cutaneous amyloidosis If 1 0 cc of a 1 5 per cent solution of Congo red is injected subcutaneously, or 0 1 cc intradermally, into the affected *region, the areas in which amyloid is deposited will be stained strongly with red dye* after from 24 to 48 hours whereas the interposed skin will appear only very slightly stained (Nomland, Dostrovsky and Sagher) In histologic sections stained with hematoxylin and eosin amyloid appears as l

tint clefts, probably becau

process of fixation With the Van Gieson stain, amyloid stains yellow and collagen red Amyloid is a protein polysaccharide complex and therefore it stains at least in lichenoid amyloidosis and in secondary amyloidosis red with Congo red, purple red with methyl violet (indicating metachromasia) and deeply red with the periodic acid Schiff reaction In primary systemic amyloidosis, however, these *staining reactions are not always present and vary* from patient to patient and even from organ to organ, probably because of differences in the amount of polysaccharides or in the nature of the union between the protein and the carbohydrate molecules (Goltz)

PRIMARY SYSTEMIC AMYLOIDOSIS

Mesenchymal tissue is affected while the parenchyma of parenchymatous organs is spared Amyloid deposits are found mainly in the smooth and striated musculature in the small blood vessels and in the gastro intestinal tract Macroglossia has been present in almost one half, *and cutaneous lesions in about one fourth*, of the 57 cases reported up to 1949 (Dahlin)

Of interest is the frequency with which primary systemic amyloidosis is associated with multiple myeloma and Bence Jones proteinuria (Brunsting and MacDonald) Examination of the urine for Bence Jones *protein, roentgenograms of the bones* and sternal biopsy in search of atypical plasma cells in the bone marrow, therefore, should be performed in all cases of primary systemic amyloidosis

about capillaries (Nomland) In some cases a mild chronic inflammatory infiltrate will be found

Differential Diagnosis Lichenoid amyloidosis must be differentiated from colloid milium For differential diagnosis see page 165

Secondary Systemic Amyloidosis

This condition occurs in chronic suppurative diseases, such as tuberculosis and in chronic cachectic diseases associated with marked loss of protein from the body Amyloid deposits are found in the parenchymatous organs especially in the liver, the kidney, the spleen (sago spleen) and the adrenals The skin is involved very rarely Michelson and Lynch have reported a case of secondary systemic amyloidosis due to tuberculosis in which there were diffuse nodular lesions of the lips due to deposits of amyloid

CALCINOSIS CUTIS

Two forms of calcinosis cutis exist metastatic and *metabolic* calcification

Metastatic Calcification

Metastatic calcification develops as a result of hypercalcemia The hypercalcemia may be due to parathyroid neoplasm hypervitaminosis D chronic renal disease or destruction of bone in such conditions as osteomyelitis and malignant growths (Mulligan) *Calcium is apt to be deposited in organs in which the cells excrete acid and therefore have a low carbon dioxide tension* As a result of the lo [illegible]

[illegible] cells of these organs excrete acid substances The skin and the subcutaneous tissue are affected only rarely However instances of metastatic calcification of either skin or subcutaneous tissue have been reported as caused by parathyroid neoplasm (Penecke Laubmann) by hypervitaminosis D (Bevans and Taylor) by chronic renal disease (Platt and Owen) and by osteomyelitis (Weidman and Shaffer)

Histopathology Calcium deposits are recognized easily in histologic sections since they stain deeply blue with hematoxylin and eosin and black with von Kossa s stain for calcium In most instances of metastatic calcification the calcium occurs as individual granules as well as massive deposits in the dermis and in the subcutaneous fat (Fig 136) Larger deposits often evoke a foreign body reaction so that giant cells an inflammatory infiltrate and fibrosis may be present around them In Weidman and Shaffer s case the calcium deposits consisted of small granules which were found not only in the

Clinically, the skin shows discrete and coalescing papules and nodules which are semitranslucent and of a waxy, amber color In addition, yellowish plaques resembling those of xanthomatosis are present. Petechiae and ecchymoses frequently occur at the site of eruption Itching is absent The face is predominantly affected especially the periorbital regions

Histopathology. Histologic examination of the skin reveals large faintly eosinophilic, amorphous masses of amyloid which may be deposited anywhere in the dermis (Fig 134) as well as in the sub cutaneous tissue In addition, small deposits of amyloid may occur in the membrana propria of the sweat glands around blood vessels and in the walls of blood vessels. In most cases, no inflammatory re action is present (Michelson and Lynch), but, in some cases, one finds foci of lymphocytes, plasma cells and foreign body giant cells (Pearson, Rice and Dickens)

In the subcutaneous tissue, one may find besides large masses of amyloid and deposits of amyloid in the walls of the blood vessels so called amyloid rings which are formed by the deposition of amyloid around individual fat cells (Fig 135) (Pearson, Rice and Dickens) The fat cells thus appear as if cemented together by the eosinophilic amyloid substance (Iverson and Morrison)

Not only in the skin and the subcutaneous tissue, but also through out the body, the small arteries and the veins show amyloid deposits often entirely replacing their media and adventitia The vessels of the tongue the skeletal muscle the respiratory tract, the heart and the gastro intestinal and the genito urinary tracts usually are affected most severely In the skeletal muscle and in the tongue, numerous muscle fibers show amyloid deposits in the form of amorphous nodu lar swellings (Iverson and Morrison)

Primary Localized Amyloidosis of the Skin (Lichenoid Amyloidosis)

In this form of amyloidosis only the skin is involved The lesions are seen most commonly on the legs but they may occur elsewhere They consist of closely set discrete conical or flat, brownish red papules which resemble the papules of lichen planus Occasionally the papules have a translucent appearance *In some instances the papules, by coalescence form plaques which may develop a verrucous surface and then resemble lichen simplex chronicus The lesions usually itch severely in contrast with those of primary systemic amyloidosis*

Histopathology. The amyloid deposits are much *smaller in size* than those found in primary systemic amyloidosis and are limited to the subepidermal region of the dermis The earliest deposits occur

In sclerodermic calcinosis, the histologic appearance of the skin and the subcutaneous tissue is that of scleroderma The calcium deposits are usually located within areas of sclerotic collagen The deposition of calcium probably is due to the decreased metabolic activity in the sclerotic tissue Decreased metabolic activity causes the carbon dioxide tension in the tissue to be lower than normal and thus reduces the solubility of calcium (Brody and Bellin)

In patients with idiopathic calcinosis cutis no perceptible histologic changes may precede the deposition of the calcium (Epstein Bauer Marble and Bennett) Bauer, Marble and Bennett found, in their case that the initial lesion consisted of deposition of finely divided particles of calcium salts around apparently normal fat cells in the subcutaneous tissue The granules seemed to coalesce slowly to form large masses Other authors found that, even in idiopathic calcinosis, mild degenerative changes preceded the deposition of calcium (Rothstein and Welt Atkinson and Weber)

GOUT

Gout is a disturbance of purine metabolism characterized by arthritis. Deposits of urates are found in the tissues of the joints particularly their cartilages in the cartilage of the ears and in the



Fig 137 Gout Deposits of sodium biurate are surrounded by a foreign body giant cell reaction On the left the sodium biurate is present as needle shaped crystals (×100)

dermis but also in the epidermis, in the sweat glands, in the sweat ducts and in the nerve trunks

Metabolic Calcification

Metabolic calcification is due to local metabolic disturbances and is not associated with hypercalcemia Deposits of calcium occur, as a rule, only in the skin and the subcutaneous tissue, but occasionally

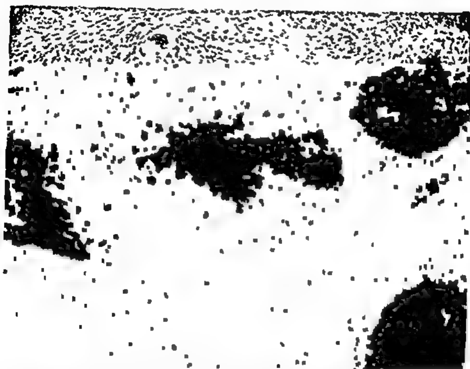


Fig 136 Metastatic calcification as a result of hypercalcemia (produced by prolonged and excessive administration of vitamin D) Von Kossa stain for calcium Irregular masses of calcium surrounded by a foreign body giant cell reaction are present in the subcutaneous fat (×100)

also in the muscles and the tendons The internal organs are spared There may be just a few deposits (calcinosis circumscripta) or innumerable deposits everywhere in the skin (calcinosis universalis) Between 30 and 40 per cent of the cases of calcinosis circumscripta and universalis described in the literature occurred in patients with scleroderma or dermatomyositis (Atkinson and Weber) (See ' Scleroderma," page 310, and Dermatomyositis page 303) In the rest, no reason for the calcinosis was evident

Histopathology. As in metastatic calcification, the calcium may be present as individual granules or as massive deposits in the dermis and in the subcutaneous fat In the subcutaneous fat, extensive areas of calcification may be observed A foreign body giant cell reaction is often found around the larger deposits of calcium

In the delayed cutaneous form the bullae arise as pressure bullae (see page 66) subepidermally (Zeligman and Baum Robert) However due to regeneration of the epidermis older bullae may be located partially or entirely within the epidermis The bullae, thus, do not differ histologically from those observed in epidermolysis bullosa The milia like those of epidermolysis bullosa dystrophica consist of small intradermally located epidermal cysts (Robert)

MYXEDEMA

Three types of myxedema occur generalized myxedema circumscribed myxedema and papular myxedema Generalized myxedema is a manifestation of hypothyroidism Circumscribed myxedema is associated with or preceded by hyperthyroidism and occurs almost invariably together with exophthalmos commonly it follows thyroidectomy or therapy with thiouracil Papular myxedema is not associated with any disturbance of thyroid function

The mucin present in the tissue in these three diseases appears light blue on staining with hematoxylin and eosin It stains red with the periodic acid Schiff reaction and is strongly metachromatic with methylene blue thionine cresyl violet and toluidene blue indicating that it is a protein polysaccharide complex (Brewer) The mucin is digested in sections by hyaluronidase which points to the fact that it contains a large amount of hyaluronic acid (Palitz and Brunner) It also stains red with mucicarmine (The latter staining method requires fixation with absolute alcohol—see page 29)

Generalized Myxedema

Clinically the entire skin appears swollen dry pale and waxy It feels firm to the touch In spite of its edematous appearance the skin does not pit on pressure The facies is characteristic the nose is broad and thick and the lips are swollen

Histopathology The dermis is increased in thickness The collagen bundles as well as the individual fibers of the collagen bundles are separated by edema The collagenous fibers show signs of degen

of mucin is usually small (Reuter)

Circumscribed Myxedema

The lesions usually are limited to the anterior aspects of the legs They consist of hard raised nodular yellow waxy plaques with prominent hair follicles

subcutaneous tissue The deposits in the ears and in the skin manifest themselves as nodules of varying size These nodules are called tophi

Histopathology. The tophi show needle shaped crystals of sodium biurate lying closely packed in the form of bundles or sheaves The crystals often have a brownish color They stain well with von Kossa's stain The accumulations of urates are surrounded by granulation tissue containing many foreign body giant cells (Fig 137)

PORPHYRIA

Porphyria represents an inborn metabolic error in which large amounts of uroporphyrin and coproporphyrin are excreted in the urine Three forms of porphyria exist the congenital form the acute intermittent form and the delayed cutaneous form In the congenital form, the porphyrins are formed in the bone marrow (porphyria erythropoietica) while in the acute intermittent form and in the delayed cutaneous form they are formed in the liver (porphyria hepatica) (Watson)

In the congenital form, cutaneous lesions identical with those seen in hydroa vacciniforme appear from earliest childhood on the exposed portions of the skin following exposure to the sun The lesions result in scarring and mutilation The teeth may appear red

The acute intermittent form starts in adult life and is characterized by attacks of abdominal pain peripheral neuropathy and mental disturbances Cutaneous lesions do not occur, as a rule However, in rare instances, cutaneous lesions like those in the delayed cutaneous form have been observed (Nesbitt and Watkins)

The delayed cutaneous form (porphyria cutanea tarda) like the acute intermittent form, remains latent until adult life Frequently chronic alcoholism by causing hepatic dysfunction precipitates the onset of clinical manifestations Blisters form on exposure to light as well as on minor mechanical or thermal trauma They often heal with scarring and formation of milia Abdominal pain and nervous system manifestations as in the acute intermittent type may be present, although to a lesser degree (Brunsting and Mason) Because of the occurrence of blisters following trauma and the presence of milia, some authors have referred to the lesions as acquired epidermolysis bullosa However the excretion of uroporphyrin and coproporphyrin in the urine and the presence of sensitivity to light make it evident that the disease is not related to epidermolysis bullosa (Brunsting and Mason)

Histopathology In the congenital form the vesicles have the same appearance as in hydroa vacciniforme (see page 46)

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PAPULAR MYXEDEMA (PAPULAR MUCINOSIS)

There is a widespread eruption of asymptomatic soft, yellowish papules which may coalesce into irregular patches

Histopathology The appearance of the mucinous infiltrate is like that in circumscribed myxedema inasmuch as there are rather large amounts of mucin as well as stellate cells (Dalton and Seidell) However the extent of the mucinous infiltrate is more limited than in circumscribed myxedema because it is present only in the upper dermis and in the case of individual papules within relatively small areas

SCLEREDEMA ADULTORUM (BUSCHKE)

Scleredema adultorum is characterized by diffuse edema and induration of the skin and the subcutaneous tissue Its cause is unknown but it is noteworthy that it frequently follows an infectious disease such as grippe or tonsillitis It usually begins on the face and spreads rapidly to involve the neck and the upper trunk Complete resolution takes place in a few months The occurrence of pleural and pericardial effusions and of hydrarthrosis has been reported (Vallee)

Histopathology Throughout the dermis one observes swelling and splitting up of the collagen bundles by edema The edema may be severe enough to produce in the dermis clear unstained spaces of various sizes (fenestration) Freund noted that the edema substance which did not stain with hematoxylin and eosin stained metachromatically with cresyl violet like mucin but not with mucicarmine Vallee found this staining reaction in one case but *not in* another Braun Falco observed purplish metachromasia with toluidene blue which was no longer present when the *sections prior to the staining* were incubated with hyaluronidase He concluded that the edema substance consisted of hyaluronic acid

ADDISON S DISEASE

Addison s disease which is caused by hypofunction of the adrenal glands is characterized by *weakness* loss of weight low blood pressure and diffuse *hyperpigmentation of* the skin and the mucous membranes

The hyperpigmentation in *Addison s disease* ...

... is that in Addison s disease the damaged adrenal gland responds but weakly to pituitary stimulation and

Histopathology. Large amounts of mucin are present in the dermis particularly in the lower dermis There it occurs not only as individual threads and granules, but also as massive deposits causing wide separation of the collagenous fibers (Fig 138) The number of

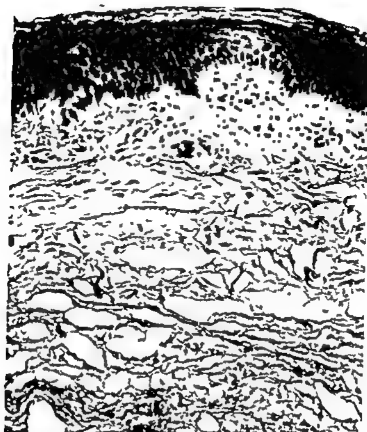


Fig 138 Circumscribed myxedema Considerable amounts of mucin are present especially in the lower dermis separating the collagen bundles as well as individual collagen fibers (*The empty spaces are due to* shrinkage and falling out of mucin) (×200)

fibroblasts is increased and newly formed collagen is present Some fibroblasts have a stellate shape and are surrounded by mucin Because of the much larger amount of mucin and the new formation of collagen, the dermis is greatly thickened, much more than in generalized myxedema

The epidermis shows hyperkeratosis The rete ridges are often flattened The vessels in the upper dermis are dilated and surrounded by a mild inflammatory infiltrate Elastic tissue stains show the elastic tissue to be frayed and greatly decreased (O Leary)

Differential Diagnosis Differentiation of acanthosis nigricans from nevus verrucosus may be impossible (Curth) As a rule however nevus verrucosus shows more marked acanthosis than acanthosis nigricans and overdevelopment rather than atrophy of the rete ridges

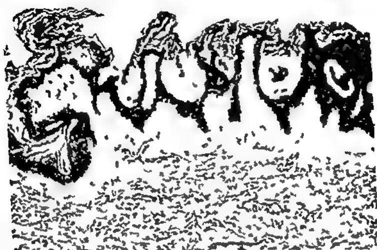


Fig. 139 Acanthosis nigricans There are hyperkeratosis and papillomatosis Several papillae project upward as finger like projections As is usually the case acanthosis and hyperpigmentation are slight (×100)

RIEHL'S MELANOSIS MELANODERMATITIS TOXICA POIKILODERMA RETICULARE (CIVATTE)

Riehl's melanosis and melanodermatitis toxica have the same appearance clinically as well as histologically (Storck) In both conditions one observes ill defined symmetrical bluish brown hyperpigmentation of the face and occasionally also of the neck and the chest There may be slight atrophy of the skin and follicular hyperkeratosis The cause of Riehl's dermatosis is not fully known but it has been suggested that it is caused by a lack of vitamin B and provoked by exposure to the sun and that thus it is related to pellagra (Poehlmann) Melanodermatitis toxica is due to contact of the affected skin with tars oils or greases

Poikiloderma reticulare differs from these two diseases clinically by its predominant localization on the neck the reticular arrangement of the hyperpigmentation and the presence of telangiectases (Pierini and Bosq) Histologically the telangiectases usually are not sufficiently evident to differentiate poikiloderma reticulare from the other two diseases

consequently, as a compensatory phenomenon, the pituitary gland is overactive.

Histopathology. Histologic examination often shows no changes other than hyperpigmentation. Occasionally, one observes slight flattening of the rete ridges and slight thinning of the epidermis. The amount of melanin is increased in both the epidermis and the dermis. In the epidermis, the melanin is present chiefly in the basal layer, but may be found also in the lower layers of the stratum malpighii. Because the pigment formation proceeds slowly over a long period of time, the number of clear cells is increased only slightly. In the upper dermis, a moderate number of melanin-laden chromatophores (melanophores) are present. There is no inflammatory reaction in the dermis.

Differential Diagnosis. A diagnosis of Addison's disease cannot be made from histologic sections, because the same histologic picture is observed in nonspecific hyperpigmentation of the skin and in the normal skin of the Negro.

ACANTHOSIS NIGRICANS

Three types of acanthosis nigricans exist: malignant acanthosis nigricans, benign acanthosis nigricans and pseudo-acanthosis nigricans. Clinically and histologically, the three forms look alike (Curth).

The malignant form occurs in adults and is associated with internal cancer, usually of the glandular type. The benign or juvenile form may start at any time before puberty. It represents a genodermatosis related to nevus verrucosus. Pseudo-acanthosis nigricans occurs in the body creases of obese, brunette persons. It disappears when the patient loses weight.

Clinically, all three forms of acanthosis nigricans present verrucous, hyperpigmented patches, predominantly in the axillae, on the neck and in the submammary and the genital regions.

Histopathology. Histologic examination reveals marked hyperkeratosis and papillomatosis. In addition, acanthosis and hyperpigmentation are present but are slight (Fig. 139). Thus, the name acanthosis nigricans has little histologic justification.

In a typical lesion, the papillae project far upward as finger-like projections and are covered with a not unduly thickened stratum malpighii. The valleys between the finger-like projections are filled in largely by keratin. In areas where there is no papillomatosis the epidermis shows areas of moderate acanthosis with adjacent areas of atrophy of the stratum malpighii. The rete ridges, as a rule, are developed only poorly. There may be a slight increase in the amount of melanin in the basal layer.

VITILIGO

Vitiligo is characterized by variously sized and shaped sharply demarcated patches of depigmentation surrounded by hyperpigmented skin

Histopathology In the depigmented areas the epidermis is devoid ... cells ... ntain ... the amount of melanin in the basal layer is increased and numerous melanophores are present in the upper dermis

The dopa reaction is negative in the basal layer of the depigmented areas and positive in the basal layer of the adjoining hyperpigmented areas

HEMOCHROMATOSIS (BRONZE DIABETES)

This disturbance of the metabolism is characterized by deposition of hemosiderin in various organs of the body The presence of hemosiderin causes bronzing of the skin cirrhosis of the liver and sclerosis of the spleen and the pancreas Sclerosis of the pancreas is responsible for the diabetes usually associated with the disease

Clinically the pigmentation of the skin is diffuse and is indistinguishable from that seen in Addison s disease

Histopathology Granules of hemosiderin are found within chromatophores in the upper dermis and in the membrana propria of the sweat glands Occasionally they may also occur in the basal cells of the epidermis Hemosiderin is best demonstrated by *staining sections* with potassium ferrocyanide With this method hemosiderin granules on account of their content of iron stain blue Not infrequently melanin is present in excess in the basal layer and within chromatophores

In selecting a site for biopsy it is not necessary to choose a pigmented area because hemosiderin is present throughout the skin in hemosiderosis However it is important not to take a *specimen* from the legs where deposits of hemosiderin frequently occur in association with stasis dermatitis and other vascular disturbances (Montgomery and O Leary)

Differential Diagnosis It is impossible to *differentiate* the granules of hemosiderin from those of melanin in routine stains They *can* however be easily differentiated by staining *with* potassium ferrocyanide which stains hemosiderin blue but does *not* stain melanin Furthermore melanin does *not* occur *in* the membrana propria of the sweat glands

Histopathology. The clinically visible hyperpigmentation in these three diseases is brought about by pigmentary incontinence of the basal layer, resulting in an accumulation of melanin in the upper dermis The epidermis shows mild hyperkeratosis, thinning of the stratum malpighii and varying degrees of degeneration of the cells in the basal layer The amount of melanin in the basal layer is de creased The papillary and the subpapillary layers of the dermis how

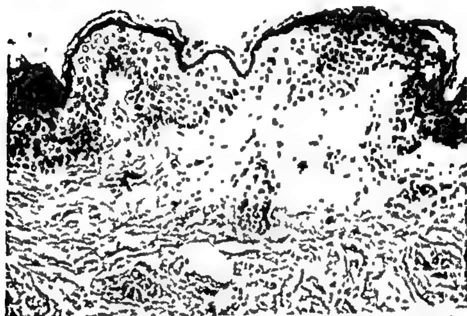


Fig 110 Melanodermatitis toxica The basal layer shows numerous clear cells The upper dermis shows large amounts of melanin mainly within but also outside of chromatophores A mild perivascular inflammatory in filtrate is present (×200)

ever, show large amounts of melanin, mainly within, but also outside of, chromatophores (Fig 110) In addition, there are various degrees of inflammatory reaction in the upper dermis In some cases, the in flammatory infiltrate is limited to the perivascular areas, in others, it is extensive, bandlike and close to the epidermis and thus re sembles that of lichen planus (Storck)

At a later stage, the degeneration of the basal layer is slight and many clear cells may be present The degree of inflammation lessens with the age of the lesion

Differential Diagnosis Incontinentia pigmenti differs from the three diseases just discussed by showing no inflammatory infiltrate in the upper dermis Addison s disease shows no inflammatory infiltrate either and only a slight amount of melanin in the dermis

there may be considerable regeneration of the cutaneous appendages (Steffens, Bair and Sheard).

Differential Diagnosis. Differentiation of phrynoderma from ichthyosis may be difficult. As a rule, however, ichthyosis shows atrophy or absence of the granular layer, thinning of the epidermis and elongation and branching of the rete ridges. Pityriasis rubra pilaris differs from phrynoderma by showing, in addition to hyperkeratosis and follicular plugging, spotted parakeratosis, irregular acanthosis and a more pronounced inflammatory infiltrate not limited to the hair follicles.

PELLAGRA

Pellagra is caused by a deficiency of the vitamin B complex but particularly of nicotinic acid. Besides cutaneous lesions, pellagra usually presents also a stomatitis which is characterized by edema and redness of the tongue and atrophy of the lingual papillae. In addition, gastro-intestinal symptoms and nervous and mental changes may be present.

Cutaneous lesions occur predominantly on exposed areas, such as the dorsa of the hands, the wrists, the face, the V area of the upper chest and the dorsa of the feet. In the early stage there is erythema which in severe cases may be accompanied by bullae. Later, the erythema assumes a livid shade and the skin becomes thickened and scaling. Ultimately, the affected areas become atrophic and deeply pigmented.

Histopathology. Early lesions present a chronic inflammatory infiltrate with moderate edema in the upper dermis. Vesicles and bullae may be present. They may be located intra-epidermally as well as subepidermally.

Older lesions show hyperkeratosis with areas of parakeratosis and a moderate degree of acanthosis. Follicular plugging occasionally is observed. The amount of melanin in the epidermis is increased. The [illegible] deeper portions of the dermis (Moore, Spies and Cooper).

In the end stage, hyperkeratosis and hyperpigmentation are still present, but the stratum malpighii now shows considerable atrophy with flattening of the rete ridges. The dermis shows moderate fibrosis.

Differential Diagnosis. The histologic picture of pellagra is not diagnostic. As a rule, it is merely one of chronic dermatitis. In the end stage, the presence of hyperpigmentation and of atrophy of the stratum malpighii serves to distinguish pellagra from chronic dermatitis.

The granules of silver, present in argyria, are also frequently located in the membrana propria of the sweat glands, but they differ from those of hemosiderin by being much smaller and more uniform in size. Furthermore, they do not stain with potassium ferrocyanide and are refractile with dark field illumination (see page 153)

OCHRONOSIS

In ochronosis, due to an inborn metabolic error, the catabolism of tyrosine cannot proceed beyond homogentisic acid. The disease is characterized by blackening of the cartilages and by osteo arthritis and may show bluish discoloration of the sclerae and brown or bluish mottled pigmentation of the skin. The urine darkens on exposure to the air. The discoloration of the cartilages, the sclerae and the skin as well as the darkening of the urine, are due to the presence of homogentisic acid which by oxidation is converted into a dark-colored insoluble product.

Histopathology. Varying amounts of a light brown pigment are present in the dermis. The pigment is either diffusely distributed or present as clumps of varying size and shape. The clumps may be large, measuring more than 100 microns in diameter. The pigment does not stain with silver nitrate as melanin does but becomes black when stained with polychrome methylene blue (Laymon).

VITAMIN A DEFICIENCY (PHRYNODERMA)

Vitamin A plays an important part in the metabolism of the epithelial structures of the skin and the mucous membranes. In addition to cutaneous changes, deficiency of vitamin A may cause night blindness, xerophthalmia and keratomalacia.

The cutaneous changes, to which the name phrynoderma has been given, consist of dryness and roughness of the skin and the presence of follicular hyperkeratosis.

Lichen spinulosus of Crocker is probably identical with phrynoderma (Lehman and Rapaport).

Histopathology. The skin shows moderate hyperkeratosis with marked distention of the upper part of the hair follicles by large horny plugs. In contrast with ichthyosis the granular layer is present and may even be increased in thickness. The lower part of the hair follicles is atrophic and usually surrounded by a slight, chronic inflammatory infiltrate. There are only few remnants of sebaceous glands. In addition, one may find evidence of atrophy of the sweat glands, such as flattening of the secretory cells (Frazier and Hu). In severe cases the sweat glands and the sebaceous glands may undergo keratinizing metaplasia (Bessey and Wolbach). When adequate amounts of vitamin A are supplied to a patient with phrynoderma,

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VITAMIN C DEFICIENCY (SCURVY)

Scurvy, caused by a deficiency of ascorbic acid, is characterized by bleeding and spongy gums and petechial hemorrhages which often are perifollicular.

Histopathology. Scurvy is characterized by inability of the supporting tissues to produce and maintain intercellular substances (Wolbach and Howe). Thus, the endothelial cells of capillaries fail to form adequate amounts of intercellular ground substance. Extravasation of red blood cells results. The extravasation occurs without inflammatory changes around the capillaries. Scurvy, consequently, belongs to the group of noninflammatory purpuras (see page 127) (Peck, Rosenthal and Erf).

Histologic examination of the skin shows hemorrhages around the capillaries. As a rule, these hemorrhages are most pronounced in the vicinity of the hair follicles. In many instances one finds hyperkeratosis and follicular plugging as in vitamin A deficiency. According to Scheer and Keil, these changes in the epidermis are purely secondary.

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17

Systemic Diseases of Unknown Cause

LUPUS ERYTHEMATOSUS

Three types of lupus erythematosus are generally recognized (1) chronic discoid lupus erythematosus (2) subacute disseminate lupus erythematosus and (3) acute systemic lupus erythematosus In [illegible] In the second type [illegible] type visceral lesions may be absent Intermediary forms between the three types occur clinically as well as histologically They cannot be regarded as separate diseases

Clinical Appearance Chronic discoid lupus erythematosus is limited usually to the face, where the flush areas of the cheeks are affected predominantly The scalp and the ears also may be involved The lesions consist of well defined erythematous slightly infiltrated patches showing adherent keratotic scaling and follicular plugging Older lesions show in addition atrophic scarring Systemic symptoms are absent

Subacute disseminate lupus erythematosus usually is superimposed upon chronic discoid lupus erythematosus but may begin as such In addition to the face other areas especially the thorax and the arms and the legs are involved Systemic symptoms such as fever malaise and leukopenia are often present The lesions consist of erythematous often slightly livid patches which tend to coalesce and show only slight scaling The prognosis as to life is fairly good since development into the fatal acute form of the disease is not common

Acute systemic lupus erythematosus has severe systemic symptoms and almost invariably is fatal Even corticotropin and cortisone as a rule merely delay death because the renal lesions do not respond to these drugs Systemic symptoms often precede the cutaneous eruption and occasionally cutaneous manifestations are absent throughout the course of the disease The cutaneous eruption frequently begins on the face as a diffuse ill-defined erythema with some edema

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fore, the hyperkeratosis may not be present until after the lesion is several weeks old. Parakeratosis is usually completely absent. The keratotic plugs are found mainly in the follicular openings but occur also in the sweat ducts and independent of either. The follicles inside the dermis may contain concentric layers of keratin instead of hairs (Fig. 141). The atrophy of the stratum malpighii is not always uni-

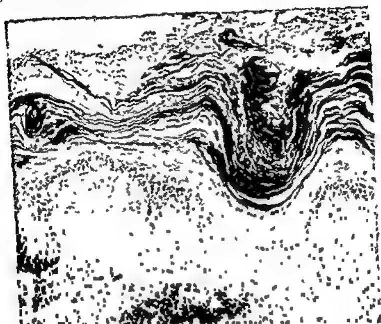


Fig. 14[illegible]
There are [illegible]
degenerati[illegible]
basophilic [illegible] of the collagen and a patchy, predominantly lymphocytic infiltrate. (×200)

form but may alternate with areas of acanthosis. Focal liquefaction degeneration of the basal layer represents the most significant histologic change in lupus erythematosus (Fig. 142). In its absence, a histologic diagnosis of lupus erythematosus is rarely, if ever, justified. In older lesions the basal layer often is partially absent as a consequence of this degeneration.

The dermis shows considerable edema in its upper portion. In darkly skinned persons melanin is often present in the upper dermis since the degeneration of the cells in the basal layer causes them to lose their melanin ("pigmentary incontinence"). The capillaries and larger vessels are dilated and their walls may show edema; however,

("erythema perstans"). *Soon other lesions appear, often widely spread over the body. They are poorly defined, purplish and often edematous, and may be purpuric or vesicular. The systemic symptoms include irregular fever, malaise, weakness, pains in muscles and joints and pleural pain. Laboratory findings include marked leukopenia, hypergammaglobulinemia, proteinuria and often hematuria*

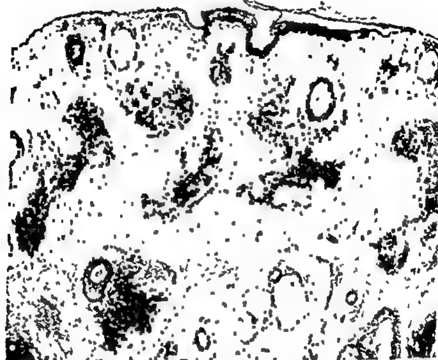


Fig. 141 Chronic discoid lupus erythematosus Low magnification There is keratotic plugging and the follicles inside the dermis contain, instead of hairs concentric layers of keratin The epidermis is atrophic and devoid of rete ridges The inflammatory infiltrate is distinctly patchy and tends to be located in the vicinity of hair follicles (×50)

In most
mbina
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skin: (1) hyperkeratosis with keratotic plugging, (2) atrophy of the stratum malpighii, (3) liquefaction degeneration of the basal cells, (4) a patchy, perivascular, c tend ency to arrangement about phic degeneration of the collagen (Fig. 141) However, not all five changes are present in every case.

The epidermal changes are secondary to those in the dermis. There-

degeneration of the collagen (see under Acute Systemic Lupus Erythematosus)

H... ...logy of Acute Systemic Lupus Erythematosus The ... fibrinoid ... ration is observed also in the skin In order to study fibrinoid degeneration of the col



FIG 143 Acute systemic lupus erythematosus The epidermis is atrophic and shows marked liquefaction degeneration of the basal layer The dermis shows fibrinoid degeneration Only a mild perivascular inflammatory infiltrate is present (×200)

lagen in the skin sections should be taken from covered areas of the body in exposed areas basophilic degeneration of the collagen ...

lagen fibers ... mally not vis... philic refract... thickened ... and more deeply eosinophilic than normally In more advanced lesions the degenerated collagen fibers become fragmented and fuse with the altered ground substance The fibrinoid material shows metachromasia upon staining with toluidine blue and stains positive with the periodic acid Schiff reaction

proliferative or obliterative changes are absent The inflammatory infiltrate is distinctly patchy. It is located mainly in the vicinity of the hair follicles and the sebaceous glands, presses upon these structures and causes their gradual atrophy and disappearance (Fig 141) The infiltrate is composed predominantly of lymphocytes but contains also a small number of plasma cells and histiocytes.

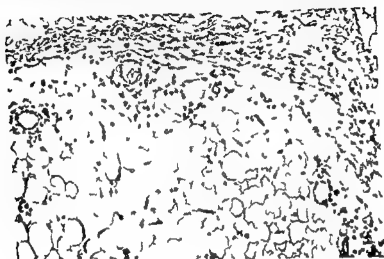
Basophilic degeneration of the collagen in the upper dermis is common in sections of discoid lupus erythematosus obtained from exposed areas (where discoid lupus erythematosus usually occurs) it is absent, however, in sections taken from covered areas (Montgomery) In spite of its common occurrence in lupus erythematosus of exposed areas, basophilic degeneration of the collagen cannot be regarded in any way as diagnostic of lupus erythematosus because it occurs also in simple senile atrophy of the exposed skin (see page 157) as well as in many other dermatoses when located in exposed areas The elastic tissue shows, irrespective of whether the section is obtained from an exposed or a nonexposed area, at first fraying and later destruction throughout the dermis wherever the inflammatory infiltrate occurs

In the differential diagnosis, two diseases have to be considered which share with chronic discoid lupus erythematosus the presence of a patchy infiltrate—namely, secondary syphilis and lymphocytic lymphoma Secondary syphilis differs from chronic discoid lupus erythematosus by the arrangement of the patchy infiltrate predominantly around blood vessels by the presence of numerous plasma cells in the infiltrate and by the presence of vascular changes In lymphocytic lymphoma the patchy infiltrate is composed entirely of lymphocytes and does not show a tendency to arrangement near the epidermal appendages Neither secondary syphilis nor lymphocytic lymphoma show epidermal changes comparable with those of chronic discoid lupus erythematosus

Histopathology of Subacute Disseminate Lupus Erythematosus The histologic changes in the lesions differ only in degree from those of chronic discoid lupus erythematosus The atrophy of the epidermis, the liquefaction degeneration of the basal cells and the edema of the dermis are more prominent than in chronic discoid lupus erythematosus whereas the hyperkeratosis and the inflammatory infiltrate are less marked

Occasionally, the edema in the upper dermis and the liquefaction degeneration of the basal cells is severe enough to result in the formation of clefts and even vesicles between the epidermis and the dermis (McCreight and Montgomery) There may be evidence of fibrinoid

fibrillary ground substance normally not visible may be present as homogeneous eosinophilic fibrinoid clumps (Fig 143) (Klemperer Pollack and Baehr 1941) There is a rather mild perivascular infiltrate In addition one sees diffusely scattered histiocytes and fibroblasts some of which show pyknosis of their nuclei Extravasations of red blood cells are frequently observed Changes in the walls of the vessels other than edema are usually absent Only oc



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casionally does one see degenerative changes in the walls They are best demonstrated by the use of the periodic acid Schiff reaction (Stoughton and Wells)

The subcutaneous fat is often involved It may show focal mucoid degeneration with reactive lymphocytic infiltration The collagen bundles separating the fat lobules may be increased in thickness and show edema and fibrinoid degeneration similar to those in the dermis (Fig 145)

Histopathology of the Visceral Lesions of *Acute Systemic* Lupus Erythematosus Visceral lesions usually are widespread but often minute in size so that they may easily be overlooked on gross inspection and even on histologic examination unless they are especially looked for The endocardium the serous membranes the heart and the skeletal muscle the renal glomeruli the spleen the lymph nodes and the fat depots are affected most commonly

Altshuler and Angevine believe that the fibrinoid material is formed by the precipitation of the acid mucopolysaccharides of the ground substance by an alkaline protein derived from either the necrosis of tissue or the interaction of the tissue with a damaging agent The fibrinoid degeneration may affect the collagenous ground substance of capillaries arterioles and venules Thus vascular damage if pres

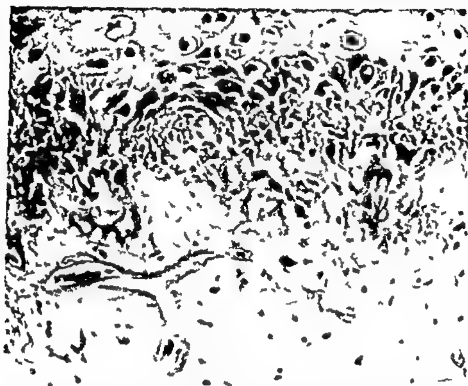


Fig 144 Acute systemic lupus erythematosus There are marked liquefaction degeneration of the basal layer and edema of the upper derm s Within the zone of subepidermal edema the collagen is present as homogeneous fibrinoid material which lies in irregular conglomerates and also surrounds a capillary (×400)

ent does not represent an independent lesion but is part of the basic injury to the collagen (Klemperer Pollack and Baehr 1941)

The histologic appearance of the skin in acute systemic lupus erythematosus resembles that of subacute disseminate lupus erythematosus (Madden Montgomery) One observes considerable liquefaction degeneration in the basal cell layer and pronounced edema in the uppermost dermis (Fig 143) Within the zone of subepidermal edema homogeneous eosinophilic fibrinoid material may be seen lying in irregular conglomerates as well as around capillaries (Fig 144) Deeper in the dermis some of the collagen bundles are swollen and stain intensely eosinophilic The inter

strated only very rarely in the blood of patients with diseases other than *acute systemic* lupus erythematosus a positive test for L. E. cells is almost pathognomonic for it (Dubois)

The formation of L. E cells is due to the presence in the plasma of a factor which causes disintegration of the nuclei of neutrophils, as well as of other cells with subsequent phagocytosis of this material by neutrophils (Haserick, Gold) The L. E cell is a neutrophil con

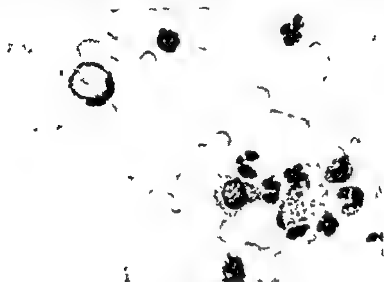


Fig 146 Acute systemic lupus erythematosus Smear of the buffy coat of a patient's blood after its incubation with heparin In the left upper corner lies an L. E cell a neutrophil containing a large smoky body In the right lower corner a rosette is seen consisting of amorphous material surrounded by phagocytizing neutrophils (×400)

taining a round structureless smoky basophilic mass of such size that it presses the lobes of the nucleus against the cell membrane (Fig 146) (Hargraves Richmond and Morton Smith) L E cells can be demonstrated most easily *in smears* made from the buffy coat of the patient's *blood* after its *incubation with heparin* (Dubois) Smears of the buffy coat of *heparinized* sternal marrow may also be used The smears are stained with Wright's stain In addition to L E cells

n

o1 ... the rosettes are precursors of the L. E cell (Haserick)

The hematoxylin staining bodies are found in various organs, especially in the kidney and the *endocardium* but also occasionally in the

The verrucous endocarditis of lupus erythematosus (the so-called Libman-Sacks *syndrome) is caused by focal* fibrinoid degeneration of the subendothelial connective tissue of the endocardium and the *subsequent round cell and fibroblastic* proliferation and fibrosis Since fibrinoid degeneration occurs again and again in the newly *formed fibrous tissue considerable* amounts of granulomatous tissue are formed resulting in raised verrucous formations (Libman and Sacks Belote and Ratner Gross Klemperer Pollack and Baehr 1941)

The serous membranes such as the pleura the epicardium and the peritoneal covering of the liver and the spleen may show fibrinoid degeneration of their collagen with mild, reactive inflammation composed of lymphocytes, plasma cells histiocytes and fibroblasts (Klemperer Pollack and Baehr 1941)

The myocardium and less frequently the skeletal muscle may show small foci of degeneration in the interfascicular connective tissue and in the muscle bundles usually associated with a mild reactive inflammation These changes are identical with those of dermatomyositis though much milder (Klemperer Pollack and Baehr 1941 Jager)

The renal glomeruli not infrequently present wire loop lesions In this type of lesion individual glomerular loops appear thickened rigid and deeply eosinophilic because of fibrinoid degeneration and thickening of the basement membrane of glomerular capillaries (Klemperer Pollack and Baehr 1941 Jager) In addition small foci of necrosis may occur in some of the glomeruli (Jager)

Periarterial fibrosis of the central arteries in the spleen is one of the most common lesions in acute systemic lupus erythematosus Thick concentrically layered rings of sclerotic collagen fibers surround these arteries (Klemperer Pollack and Baehr 1941 Kaiser)

The lymph nodes often show foci of necrosis

The body fat may show the same changes as those *described for* the subcutaneous fat

Vascular changes are usually not conspicuous Occasionally however the fibrinoid degeneration affects the collagenous ground substance of blood vessels In rare instances vascular changes are marked and resemble those of periarteritis nodosa (Jarcho Mallory) *It is* possible that in these cases lupus erythematosus and periarteritis nodosa are present simultaneously

Two structures are encountered frequently in acute systemic *lupus* erythematosus L E cells in the blood and hematoxylin staining bodies in the tissue They are absent in chronic discoid and *chronic* disseminated lupus erythematosus Since L E cells can be demon

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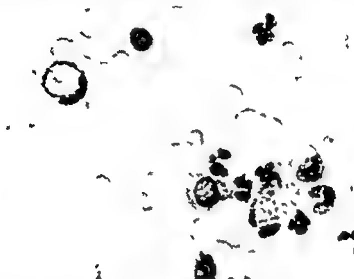


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Lupus Erythematosus Profundus (Kaposi Irganc)

In this rare condition cutaneous lesions of chronic discoid lupus erythematosus are present and in addition one or more firm sharply outlined movable subcutaneous nodes covered by normal appearing skin

s that because subcutaneous

sarcoid of Darier Roussy He concludes that lupus erythematosus profundus constitutes a coexistence of two different diseases—discoid lupus erythematosus and subcutaneous sarcoid of Darier Roussy

DERMATOMYOSITIS

In dermatomyositis the skin and the skeletal muscles are predominantly affected

The cutaneous lesions consist of extensive rather sharply defined areas of erythema and edema involving predominantly the face the chest and the arms The eruption often greatly resembles that of subacute or acute lupus erythematosus The lesions in the muscles cause progressive weakness with vague muscular pain and later atrophy of the muscles Involvement of the esophagus often results in dysphagia Prior to the use of corticotropin or cortisone the disease was often fatal Even with its use atrophy and fibrosis of the skin and the muscles may result producing a clinical picture resembling that of generalized scleroderma

Histopathology In the skin particularly in early lesions the histologic changes may resemble those of subacute disseminate lupus erythematosus (Kinney and Maher O Leary and Waisman) Not infrequently however the histologic picture is that of a nonspecific chronic dermatitis In old lesions the collagen bundles of the dermis may show thickening homogenization and sclerosis and the cutaneous vessels fibrotic thickening of their walls so that the changes are indistinguishable from those of scleroderma (Dowling Freudenthal)

The subcutaneous fat may show mucoid degeneration of the fat cells and focal lymphocytic infiltration in the early stage and areas of fibrosis and calcification in the late stage (Norregaard Wainger and Lever) (see Calcinosis Cutis page 276)

During the active phase of the disease the skeletal muscles show

skin (Klemperer, Gueft, Lee, Leuchtenberger and Pollister, Gueft) They appear in sections stained with hematoxylin and eosin as red purple, homogeneous bodies *of the size and the shape of fibroblasts* or histiocytes They may be present singly or in aggregates They develop from degenerating nuclei and are identical with the smoky body within L. E cells Occasionally, one may see histiocytes or neutrophils which have phagocytized a hematoxylin staining body The similarity of these cells to L. E cells is striking Histochemical investigations have shown that, in the smoky bodies of L. E cells *and in the hematoxylin staining bodies*, the Feulgen reaction for desoxyribonucleic acid (DNA) is positive This is evidence that they are derived from nuclear chromatin (Gueft)

Relationship of Acute Systemic Lupus Erythematosus to Dermatomyositis and Generalized Scleroderma. These three diseases—lupus erythematosus, dermatomyositis and scleroderma—are related to one another (Banks) The fundamental pathologic lesion, namely fibrinoid degeneration of the collagen, is the same in all three diseases (Klemperer, Pollack and Baehr, 1941, Baehr and Pollack) Only *the response to the fundamental lesion and the organs* affected differ in these three diseases One may summarize the response to fibrinoid degeneration of the collagen in these three diseases as follows

In lupus erythematosus, the degeneration is associated with mild inflammation, occurring, as a rule, in small foci The lesions are widespread

In dermatomyositis, the degeneration is associated with usually pronounced inflammation Lesions are present mainly *in the* skin and the striated musculature, but other organs, particularly the heart may be involved

In scleroderma the degeneration is associated with only slight inflammation but with marked fibrosis As in dermatomyositis the principal lesions are in the skin and the striated musculature In many cases, other organs (such as the heart the esophagus, the lungs and the kidneys) are involved also

The cause of fibrinoid degeneration of the collagen in these three diseases *is not known It is assumed* by *some* that the degeneration represents an allergic or hyperergic, reaction to infection, particularly streptococcal infection However, Klemperer, Pollack and Baehr (1942) point out that, although fibrinoid degeneration of the collagen may occur in hypersensitivity reactions, it does not necessarily follow that all instances of fibrinoid degeneration are on the basis of hypersensitivity.

In older lesions the changes in the muscles may resemble those of scleroderma The muscle bundles show sclerosis and atrophy and fibrotic connective tissue replaces the muscle bundles in many areas On the basis of a study of these late changes as just described in the skin and the skeletal muscle several authors have concluded that dermatomyositis and generalized scleroderma represent one and the same disease (Dowling Freudenthal)

Changes in organs other than the skin and the skeletal muscles occur but not so regularly as in acute systemic lupus erythematosus or in generalized scleroderma The heart may show changes identical with those in the skeletal muscle though less severe (Kinney and Maher O Leary and Waisman Wainger and Lever) The body fat may be affected similarly as the subcutaneous fat (Greenway and Lambie Kinney and Maher Wainger and Lever) Inflammatory changes in the serous membranes may occur (Kinney and Maher) Ulcerative lesions in the gastro intestinal tract due to vascular occlusions have been described (Karelitz and Welt Horn Wainger and Lever)

Of interest is the relatively common occurrence of visceral carcinoma in patients with dermatomyositis (Dostrovsky and Sagher) So far 81 cases of carcinoma in dermatomyositis have been reported (Schuermann) In a statistical analysis Schuermann concludes that carcinoma occurs at least five times more frequently in patients with dermatomyositis than in the normal population In contrast with this only one case of carcinoma in scleroderma has ever been reported

Poikiloderma Atrophicans Vasculare (Jacobi)

Poikiloderma atrophicans vasculare has been described in a few instances as an independent disease (Marchionini and Resser Dow

As a rule

It occurs

... in dermatomyositis but also in lupus erythematosus and in mycosis fungoides (see page 481) When associated with dermatomyositis the term poikilodermatomyositis is often employed

Clinically poikiloderma atrophicans vasculare presents large ill defined areas usually in symmetrical distribution which in the early stage show erythema and slight scaling a mottled ...

... pronounced The clinical picture then resembles chronic radiodermatitis

degenerative changes and inflammation. The degree of these changes varies not only in different muscles but also within each affected muscle. *Even in severely affected muscles,* close to areas of severe damage, one often finds areas of mild degeneration and areas in which the *muscle bundles appear normal* (Fig. 147). In areas of mild degeneration, the muscle bundles exhibit effacement of transverse striation,



FIG 147 Dermatomyositis, muscle The muscle bundles show *various degrees of degeneration In addition, one sees edema* and focal collections of inflammatory cells (×100)

coagulation or hyalinization of the sarcoplasm and proliferation of nuclei. In more severely degenerated areas, the muscle bundles show fragmentation of fibers, granular and vacuolar degeneration, basophilic staining and phagocytosis by large histiocytes. Inflammatory changes are secondary and not essential; they represent a reaction to the parenchymatous damage One observes a cellular infiltrate, composed largely of lymphocytes, but containing also plasma *cells,* histiocytes and fibroblasts, between the muscle bundles, either in perivascular arrangement or distributed diffusely. In addition, *edema* usually separates the muscle bundles The blood vessels are dilated, but, as a rule, their *walls reveal no abnormalities* (O'Leary and Waisman).

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Poikiloderma Atrophicans Vasculare (Jacobi)

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Clinically poikiloderma atrophicans vasculare presents large ill defined areas usually in symmetrical distribution which in the early stage show erythema and slight scaling a mottled pigmentation and numerous telangiectases In the late stage the skin appears atrophic the erythema has largely disappeared but the mottled pigmentation and the telangiectasia are more pronounced The clinical picture then resembles chronic radiodermatitis

Histopathology In the idiopathic form of poikiloderma and in poikiloderma associated with dermatomyositis or lupus erythematosus the histologic changes are identical In the early active stage the epidermis shows moderate atrophy of the stratum malpighii effacement of the rete ridges and hydropic degeneration of the basal cells (Fig 148) In the upper dermis one finds a fairly dense cellular



Fig 148 Poikilodermatomyositis early stage The epidermis shows atrophy and hydropic degeneration of the basal cells In the upper dermis one sees a fairly dense inflammatory infiltrate which in places invades the epidermis The collagen of the upper dermis shows edema and hyalinization (×200)

infiltrate which in places invades the epidermis and often has a band like arrangement The infiltrate consists of lymphocytes histiocytes and fibroblasts Many melanophores may be present Some of the superficial capillaries are dilated The collagen is edematous and shows hyaline degeneration The elastic tissue is largely destroyed Hair follicles and sebaceous glands are absent (Horn)

In the late stage the epidermis is atrophic There is marked dilatation of superficial capillaries The dermis shows homogenization and sclerosis of the collagen with little or no inflammatory infiltrate Melanophores are present in varying numbers In contrast with scleroderma the dermis is greatly thinned (Guy Grauer and Jacob)

In poikiloderma associated with mycosis fungoides the histologic changes in the dermis are those of mycosis fungoides (see page 489)

Differential Diagnosis Subacute disseminate lupus erythematosus like poikiloderma atrophicans vasculare shows atrophy of the stratum malpighii and vacuolization of the basal layer However the presence of the superficially located bandlike infiltrate in poikiloderma atrophicans vasculare usually makes a differentiation possible

SCLERODERMA

Two forms of scleroderma occur circumscribed scleroderma (morphea) and systemic or generalized scleroderma

Clinical Appearance In circumscribed scleroderma (morphea) one or several round oval or irregularly shaped smooth indurated patches are present They are at first dull red or violaceous in color but soon assume an ivory color As long as there is peripheral extension the patches tend to have a purplish halo (lilac ring) The disease is benign Internal lesions are absent

In systemic or generalized scleroderma large areas of the skin are affected At first the involved areas present diffuse induration As the disorder progresses the skin and the subcutaneous tissue become firmly bound to the underlying structures so that motion is difficult Gradually the skin and the subcutaneous tissue undergo atrophy but even at this stage the skin retains some of its induration The face and the hands are often the most severely affected areas (acrosclerosis) In addition to the skin the striated *musculature invariably is affected* resulting in weakness and muscular atrophy Involvement of the esophagus may lead to difficulties in deglutition of the heart to cardiac insufficiency of the lungs to dyspnea

Histopathology of Circumscribed Scleroderma (Morphea) An early inflammatory and a late sclerotic stage exist Most sections obtained routinely show a histologic picture intermediary between *the two stages*

In the early lesion the collagenous bundles appear swollen and *homogeneous* They are separated by edema An inflammatory infiltrate predominantly lymphocytic *is present* between the collagenous bundles and around blood vessels (Fig 149) The walls of the vessels *are edematous* These *changes* are present throughout the dermis In addition the inflammatory infiltrate extends between the fat cells of the subcutaneous layer *causing degeneration* of the fat cells The elastic fibers are frayed and may be destroyed

In a late lesion the *dermis is markedly* thickened The collagen bundles are *hypertrophic sclerotic* and closely packed (Fig 150) Fibroblasts are fewer than *in the* normal dermis The inflammatory infiltrate has disappeared *almost completely* except around the vessels where as a rule *one still finds* a few inflammatory cells Most of

the vessels in the dermis show marked thickening and sclerosis of their walls with narrowing of their lumina Sebaceous glands and hair structures are often completely absent Sweat glands on the other hand, are still present they are reduced in number and are atrophic Instead of lying close to the cutaneous subcutaneous border and being surrounded by fat cells they lie in the midst of sclerotic

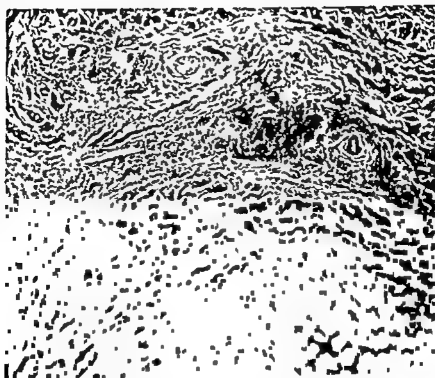


Fig 149 Scleroderma early stage The collagenous bundles appear swollen and homogeneous and are separated by edema An inflammatory infiltrate predominantly lymphocytic is present between the collagenous bundles The wall of the blood vessel seen on the right side is thickened by edema and beginning fibrosis (×100)

collagenous bundles tightly bound down by them The fact that the sweat glands lie inside the dermis rather than at its lower border is evidence that the thickening of the dermis is produced not alone by hypertrophy of the pre existing collagen bundles but also by new formation of collagen at the lower border of the dermis The border between the dermis and the subcutaneous layer is not so sharp as it usually is because thick strands of sclerotic collagen extend from the dermis into the subcutaneous layer and replace much of the subcutaneous fat The thickness of the subcutaneous layer may be greatly reduced The vessels in the subcutaneous layer, including those of large caliber, often show marked thickening of all their coats with

narrowing of the lumen (O Leary and Nomland) It is worth noting that the rete ridges of the epidermis usually remain well preserved in spite of the fact that the thickened collagen bundles extend right up to it

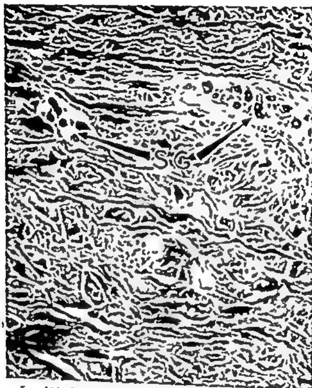


Fig 150 Scleroderma late stage The collagen bundles [illegible]

(×100) [illegible] bound down by collagen

Histopathology of Generalized Scleroderma The cutaneous changes are essentially the same as in circumscribed scleroderma so that a histologic differentiation of the two types is not possible [illegible] the early stage [illegible]
the circumscr[illegible]
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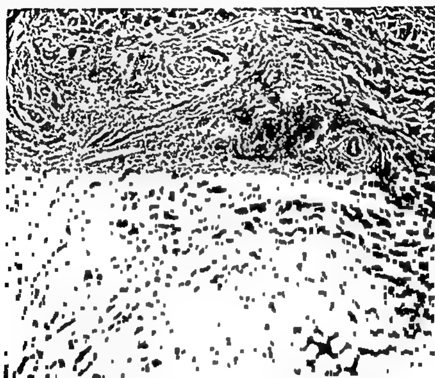
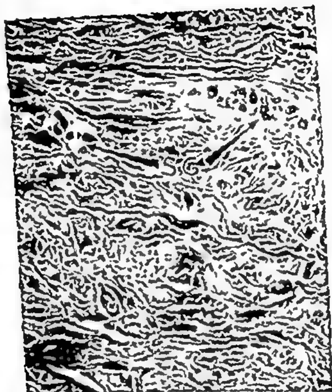


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F c 150 Scleroderma late stage The collagen bundles are hypertroph c sclerot c and closely packed together Or ly very l ttle inflamm atory infiltrate is present Fibroblasts are fe er than in tl e normal derm s Groups of rat er atrophic s eat glands (S G) are t ghtly bound do n by collagen (×100)

Histopathology of Generalized Scleroderma The cutaneous changes are essentially the same as in circumscribed scleroderma so that a histologic differentiation of the two types is not possible In the early stage degenerative changes are often more severe than in the circumscribed type One may observe fibrinoid degeneration of the collagen (Pollack) The walls of the vessels may show marked intimal proliferation fil rinoid degeneration and inflammatory in filtration (Masugi and Ya Shu) An occasional vessel may show throm

bosis. In the late stage, focal or even extensive calcification may take place in the lower dermis and in the subcutaneous layer (Talbott Gall, Consolazio and Coombs, Brody and Bellin, Kanee) (See also "Calcinosis Cutis," page 276) Also, in the late stage of generalized scleroderma, the epidermis may show, in contrast to circumscribed scleroderma, atrophy with disappearance of the rete ridges

Histopathology of the Visceral Lesions of Generalized Scleroderma. There are often extensive systemic manifestations The skeletal *muscles* are nearly always affected severely In early lesions degeneration of muscle bundles with accompanying inflammation *similar to dermatomyositis but less severe, may be observed occasionally* However, the characteristic changes are homogenization sclerosis and atrophy of the muscle bundles with increase in the interstitial connective tissue In contrast with dermatomyositis, the interseptal blood vessels often show marked obliterative changes Foci of chronic inflammation may be present around the vessels The musculature of the esophagus is often affected similarly (Lindsay, Templeton and Rothman) Extensive atrophy and fibrosis may occur in the heart muscle (Weiss, Stead, Warren and Bailey) and in the *intestinal musculature* (Bevans) *Widespread sclerosis of the medium sized and the small sized vessels in the myocardium has been observed*

Pathologic changes may occur also in the endocardium and the epicardium (Pollack), in the serous membranes (Bevans) and in the esophageal and the intestinal mucosa (Bevans) The changes consist in early lesions, of fibrinoid degeneration of the collagen with reactive inflammation, as in acute systemic lupus erythematosus In older lesions, homogenization and sclerosis of the collagen predominate

Additional findings in occasional instances include glomerulitis of the wire loop type, as in acute systemic lupus erythematosus (Pollack, Bevans) extensive fibrosis with cystic changes in the lungs (Dostrovsky), and fibrosis of the thyroid (Bevans)

PERIARTERITIS NODOSA

Periarteritis nodosa is a *manifestation of hypersensitivity* Although, in most cases, the cause of the disease is not apparent, the administration of foreign serum or of sulfonamides may be the cause (Rich) The disease affects mainly small arteries and arterioles, but occasionally also veins The principal vessels affected are those of the gastro intestinal tract, the kidneys and the heart, but those of the brain, the lungs and the skin as well as those of other organs may be involved

Depending on the sites of involvement the clinical symptoms may vary Severe abdominal pain and symptoms of nephritis and of myocardial disease are the most common manifestations Irregular fever and marked prostration are present The disease is fatal in the vast majority of cases

Cutaneous manifestations are found in about one third of the cases They are manifold and may consist of macules papules nodules petechiae ecchymoses and necrotic ulcers (Fig 151) Subcutaneous nodules usually movable and painless are observed occasionally (Ketron and Bernstein) In some cases extensive areas of cutaneous hemorrhage with subsequent necrosis occur (Melczer and Venkei)

Histopathology The name periarteritis is misleading for the lesions actually represent a panarteritis On a histologic basis the changes which occur in the arteries and the arterioles may be divided into four stages (Arkin Weir)

In the first the degenerative stage sections of the intima and the media undergo necrosis The necrosis often affects only a segment rather than the entire circumference of the vessel and only portions of the vessels are involved Miliary aneurysms may form in areas of segmental necrosis

In the second the inflammatory stage the necrotic area and the adjoining adventitia are densely infiltrated with polymorphonuclear leukocytes and eosinophils and sometimes also with lymphocytes and plasma cells (Fig 152) The infiltrate extends to the perivascular tissue The lumen of most vessels thus affected is thrombosed

In the third the granulation stage the necrotic part of the vascular wall is replaced by granulation tissue and the intima shows proliferation leading to partial or total occlusion of the lumen

In the fourth the fibrotic stage the destroyed vascular wall is replaced by scar tissue The lumen may show reduction in size obliteration or recanalization

In the skin the arterioles at the cutaneous subcutaneous border and in the subcutaneous tissue may show the typical changes of periarteritis nodosa (Fig 151) However the small blood

[illegible]

vessel walls composed largely of neutrophils and eosinophils many of which show fragmentation of their nuclei Thrombus formation with or without inflammatory reaction also may occur in the cutaneous vessels The vasculitis and the throm

bus formation cause extravasation of erythrocytes (Ketron and Bernstein).

It has been noted by several authors (Carol and Prakken, Miescher, Slinger and Starck) that periarteritis nodosa may occur in a benign,



Fig 151 Periarteritis nodosa. Low magnification An artery (A) at the cutaneous subcutaneous border shows the granulation stage of periarteritis nodosa Above the artery is an ulcer which is probably caused by the occlusion of the artery (×50)

chronic form limited to the skin and the subcutaneous tissue These authors state that, histologically, the lesions of the benign form are indistinguishable from those of the malignant systemic form

Allergic Granulomatosis

An attempt has been made recently to divide periarteritis nodosa into two types: "true periarteritis nodosa" and "allergic granulomatosis" (Churg and Strauss, Strauss, Churg and Zak; Zeek) In the

latter group allergic manifestations dominate the clinical picture to a much greater extent than in true periarteritis nodosa Most pa tients have severe asthma as the first symptom and in addition to cutaneous lesions including ra intracutaneous and sub pronounced The course is

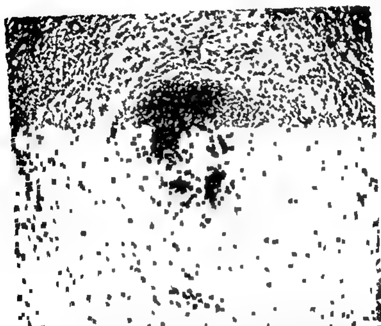


Fig 159 Periarteritis nodosa High magnification A medium sized artery located in the lower dermis shows partial necrosis of its wall and invasion by inflammatory cells (×200)

chronic and usually fatal Strauss Churg and Zak believe that peri arteritis nodosa as a result of drug sensitivity usually manifests itself as allergic granulomatosis

Histopathology Histologically in addition to typical widespread lesions of periarteritis nodosa one finds extravascular granulomas in many organs The cutaneous and the subcutaneous nodules show no necrotizing arteritis but only extravascular granulomas They con sist of areas of central necrosis surrounded by radially arranged histiocytes and foreign body giant cells which are embedded in a diffuse inflammatory infiltrate rich in eosinophils (Strauss Churg and Zak)

The purpuric lesions show the same appearance as those of ana phylactoid purpura (see page 127)

bus formation cause extravasation of erythrocytes (Ketron and Bernstein).

It has been noted by several authors (Carol and Prakken, Miescher, Slinger and Starck) that periarteritis nodosa may occur in a benign



FIG 151 Periarteritis nodosa Low magnification An artery (A) at the cutaneous subcutaneous border shows the granulation stage of periarteritis nodosa Above the artery is an ulcer which is probably caused by the occlusion of the artery (×50)

chronic form limited to the skin and the subcutaneous tissue These authors state that, histologically the lesions of the benign form are indistinguishable from those of the malignant systemic form

ALLERGIC GRANULOMATOSIS

An attempt has been made recently to divide periarteritis nodosa into two types "true periarteritis nodosa" and "allergic granulomatosis" (Churg and Strauss, Strauss, Churg and Zak, Zeek) In the

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18

Epidermal Tumors

HISTOGENESIS AND CLASSIFICATION OF EPIDERMAL TUMORS

The epidermal tumors may be divided into two classes namely tumors of the surface epidermis and tumors of the epidermal appendages In each class nevoid tumors (or hamartomas) and *carcinomas* occur

Nevoid tumors or hamartomas are defined as benign neoplasms which usually arise in accordance with the Cohnheim theory from ... may arise from immature ... ring adult life *Carcinomas* ... posed *according to Hanse*mann s theory of anaplastic cells They usually arise from mature cells due to their change into anaplastic cells but embryonal cells m ...

... are autonomous able to exist more independently than embryonal cells and therefore survive when carried away through the lymphatics and multiply as metastases

Tumors of the Surface Epidermis The tumors of the surface epidermis may be classified as follows

1 Nevoid (benign) tumors
   a Nevus verrucosus (papilloma)
   b Epidermal cyst
2 Precancerous tumors
   a Keratosis senilis
   b Leukoplakia
3 Carcinomas
   a Squamous-cell carcinoma (epidermoid carcinoma)
   b Bowen s disease (intra epidermal squamous-cell carcinoma)
   c Paget s disease

Tumors of the Epidermal Appendages The nevoid tumors or hamartomas of this group can be *divided* according to the decreasing degree of organization and differentiation observed in them into

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Nevoid tumors or hamartomas are defined as benign neoplasms which usually arise in accordance with the Cohnheim theory, from

mann's theory of anaplastic cells They usually arise from mature cells due to their change into anaplastic cells, but embryonal cells may also occasionally change into anaplastic cells and thus give rise to carcinoma Anaplastic cells are dedifferentiated cells which behave differently from embryonal cells (Foulds) They are autonomous, able to exist more independently than embryonal cells and, therefore survive when carried away through the lymphatics and multiply as metastases

Tumors of the Surface Epidermis The tumors of the surface epidermis may be classified as follows

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   a Nevus verrucosus (papilloma)
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2 Precancerous tumors
   a Keratosis senilis
   b Leukoplakia
3 Carcinomas
   a Squamous-cell carcinoma (epidermoid carcinoma)
   b Bowen's disease (intra-epidermal squamous cell carcinoma)
   c Paget's disease

Tumors of the Epidermal Appendages The nevoid tumors, or hamartomas of this group can be divided, according to the decreasing degree of organization and differentiation observed in them, into

four groups organic nevi adenomas benign epitheliomas and basal cell epitheliomas (See Table 6) The carcinomas of the epidermal appendages can be divided into sebaceous gland carcinomas eccrine gland carcinomas and apocrine gland carcinomas

The author has advanced the thesis that the organic nevi the adenomas the benign epitheliomas and the basal cell epitheliomas develop from arrested embryonal primary epithelial germ cells and, as such are primary epithelial germ tumors Since the primary epithelial germ is an embryonal structure (see Chart 1 page 4) the tumors developing from it can accordingly be regarded as nevoid tumors or hamartomas It is the author s belief that the organic nevi the adenomas and the benign epitheliomas arise from primary epithelial germ cells which prior to the onset of neoplasia attained a certain degree of differentiation whereas the basal cell epitheliomas arise from primary epithelial germ cells which attained no or only little differentiation In accordance with the potentiality inherent in the primary epithelial germ to differentiate into sebaceous glands apocrine glands and hair differentiation in the tumors developing from the primary epithelial germ can be toward either sebaceous gland apocrine gland or hair structures (see Table 6) Pinkus recently has suggested that those tumors in this group which arise in later life—especially the basal cell epitheliomas—do not necessarily arise from congenitally preformed epithelial germ rests but from immature pluripotential cells forming in later life

The organic nevi are composed of mature organic structures The cutaneous adenomas show less differentiation than the organic nevi nonetheless well developed glandlike structures are present In the benign epitheliomas there is a further step down in respect to differentiation The basal cell epitheliomas are the least differentiated of the primary epithelial germ tumors

Basal cell epitheliomas are not considered carcinomas because they do not metastasize Their origin from basal cells is doubted because their cells in contrast with basal cells do not possess intercellular bridges They are believed to originate from the primary epithelial germ for the following reasons (1) they occur only in areas where primary epithelial germ structures (sebaceous glands apocrine glands or hair) are found (2) the cells of undifferentiated basal cell epitheliomas resemble the cells of primary epithelial germs as found in embryos from 4 to 6 months old (Fig 1) (3) structures resembling sebaceous glands tubular glands and hair are present in many basal cell epitheliomas and (4) basal cell epitheliomas frequently are seen in the same lesion with primary epithelial germ tumors of higher differentiation

TABLE 6.—CLASSIFICATION OF THE NEVOID TUMORS OF THE EPIDERMAL APPENDAGES (PRIMARY EPITHELIAL GERM TUMORS)

	WITH SEBACEOUS DIFFERENTIATION	WITH APOCRINE DIFFERENTIATION	WITH HAIR DIFFERENTIATION
I Organic hamartomas (organic nevi)	Sebaceous nevi 1 Nevus sebaceus (Jadassohn) 2 Adenoma sebaceum (Pringle) 3 Senile sebaceous nevus 4 Fordyce disease	Apocrine nevi	Hair nevi
II Organoid hamartomas (adenomas)	Sebaceous adenoma	Apocrine adenomas 1 Syringocystadenoma papilliferum 2 Hidradenoma papilliferum	
III Suborganoid hamartomas (benign epitheliomas)	Sebaceous epithelioma	Apocrine epitheliomas 1 Syringoma 2 Cylindroma 3 Myo-epithelioma	Hair epitheliomas 1 Tricho-epithelioma (epithelioma adenoides cysticum) 2 Calcifying epithelioma
IV Nonorganic hamartomas a Differentiated basal cell epitheliomas	Cystic basal-cell epithelioma	Adenoid basal cell epithelioma	Keratotic basal cell epithelioma
b Undifferentiated basal cell epitheliomas	—	—	—

Some of the terms used to designate groups of tumors require definition

NEVUS This term is used in the literature in two different ways referring either to a tumor composed of nevus cells (nevocellular nevus, pigmented nevus) or to a lesion originating from embryonal cells and composed of mature or nearly mature structures (organic nevi, such as nevus vasculosus, nevus sebaceus, nevus pilosus and nevus verrucosus) In order to avoid confusion, it is advisable to use the term nevus when referring to an organic nevus always with a qualifying adjective, so that nevus without qualifying adjective designates a tumor composed of nevus cells According to Jadassohn organic nevi are tumors and not hyperplasias because they develop on the basis of an abnormal germ anlage and not by an increase in the size and number of mature structures

NEVOID TUMOR (HAMARTOMA) The term nevoid tumor is used widely as a designation for benign tumors of embryonal origin However, this term lacks conciseness and therefore is unsatisfactory The term hamartoma appears more satisfactory This term, derived from the Greek word *hamartanein* (fail, miss, err) was coined by Albrecht as a designation for tumorlike malformations showing a faulty mixture of the normal components of the organ in which they occur Van der Valk enlarged the concept of hamartoma to include all benign tumors of embryonal origin with an organoid structure Since no satisfactory term exists for the entire group of benign tumors of embryonal origin, the author has suggested that the meaning of the term hamartoma be extended to include all such tumors even those with suborganoid and nonorganic structure Thus, the tumors arising from the primary epithelial germ may be divided into organic hamartomas (organic nevi), organoid hamartomas (adenomas), suborganoid hamartomas (benign epitheliomas) and nonorganic hamartomas (basal cell epitheliomas)

EPITHELIOMA The term epithelioma is used by many authors as a synonym for carcinoma of the epidermis Since, however, the true meaning of the word is tumor of the epithelium the term may be used, as suggested by Jadassohn, as a designation of benign as well as malignant tumors of the epidermis provided that a qualifying adjective is added It would perhaps be best if, as Becker has suggested, the term epithelioma be reserved for benign epidermal tumors and carcinoma for malignant epidermal tumors

1. TUMORS OF THE SURFACE EPIDERMIS

NEVUS VERRUCOSUS

Nevus verrucosus is known also under various other clinical designations, such as hard nevus, epidermal nevus, nevus unius lateralis, linear nevus keratotic nevus and ichthyosis hystrix



Fig 153 Nevus verrucosus There are marked hyperkeratosis, acanthosis and papillomatosis The rete ridges are elongated (X50)

The lesions may be single or multiple and usually are present at birth They consist of verrucous growths of brownish color which often show linear configuration Large horny excrescences may be present

Histopathology. Nevus verrucosus shows hyperkeratosis, papillomatosis and acanthosis with elongation of the rete ridges (Fig 153) Thus, it has the histologic appearance of a papilloma

Some of the terms used to designate groups of tumors require definition

NEVUS This term is used in the literature in two different ways referring either to a tumor composed of nevus cells (nevocellular nevus pigmented nevus) or to a lesion originating from embryonal cells and composed of mature or nearly mature structures (organic nevi such as nevus vasculosus nevus sebaceus nevus pilosus and nevus verrucosus) In order to avoid confusion it is advisable to use the term nevus when referring to an organic nevus always with a qualifying adjective so that nevus without qualifying adjective designates a *tumor composed of nevus cells* According to Jadassohn organic nevi are tumors and not hyperplasias because they develop on the basis of an abnormal germ anlage and *not* by an *increase* in the size and number of mature structures

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cans These five diseases all show hyperkeratosis and papillomatosis. In typical instances, differentiation is easy, but occasionally one is unable to make any more specific diagnosis in these diseases than papilloma Because the term papilloma is often used in such non

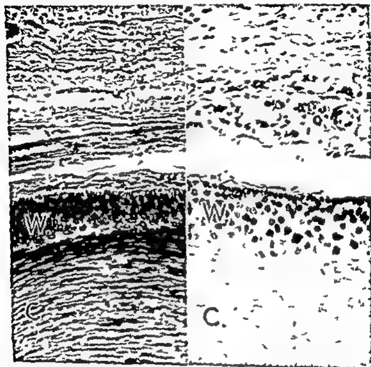


FIG 135 Comparison of epidermal cyst (*left*) with sebaceous cyst (*right*) The wall (W) of t

is filled with amorphous material which has formed by the gradual disintegration of the vacuolated cells (×200)

specific sense it is better to avoid this term as a designation for nevus verrucosus

In typical instances keratosis senilis differs from ne verrucosus
by
pro downward
ma loma shows
no

The degree of hyperkeratosis and papillomatosis differs considerably from lesion to lesion and depends on the size of the lesion The thickness of the granular layer varies, areas of marked hyperplasia of the granular layer may alternate with areas in which it is atrophic



Fig 154 Epidermal cyst The wall is composed of true epidermis i e squamous granular and horn cells The cyst is filled with keratin (×100)

There may be some proliferation of basal cells (as seen in basal-cell papilloma) and hyperpigmentation of the basal layer In rare instances apocrine gland lumina are found deep in the dermis (see page 346) Nevus cells are absent in pure nevus verrucosus However, the combination of nevus verrucosus and nevus pigmentosus is not infrequent, and in that case nevus cells are present

Differential Diagnosis Nevus verrucosus must be differentiated from other types of papillomas namely senile keratosis (keratosis senilis), basal cell papilloma verruca vulgaris and acanthosis nigri-

SEBACEOUS CYSTS, or steatomas, have a wall composed of epithelial cells that possess no intercellular bridges and do not undergo keratinization Many of the cells are vacuolated because of their transformation into sebaceous cells (Fig 155) The wall never possesses



FIG 156 Calcified sebaceous cyst The palisading of the basal layer makes it evident that this is a sebaceous cyst It has ruptured and fibrous tissue has proliferated into the lumen (×100)

rete ridges at its periphery The peripheral cell layer sho[illegible]

[illegible]

[illegible] Large amounts of cholesterol and cholesterol crystals may be present in the cysts Calcification occurs frequently within sebaceous cysts (Fig 156) As in epidermal cysts a considerable foreign body reaction results when the wall of a sebaceous cyst ruptures, and the cyst may undergo partial disinte-

203) *Verruca vulgaris* shows groups of large vacuolated cells in the upper stratum malpighii and the granular layer, and intermittent areas of parakeratosis (Figs 118, 119). *Acanthosis nigricans*, as a rule, shows less acanthosis than nevus verrucosus and atrophy of the rete ridges rather than elongation (Fig 139).

EPIDERMAL CYST (WEN), SEBACEOUS CYST, MILIUM, DERMOID CYST

Epidermal cysts and sebaceous cysts are often indistinguishable clinically *Both are commonly called wens On histologic examination*, most wens prove to be epidermal rather than sebaceous cysts In their material, Warvi and Gates found 556 epidermal cysts as compared with only 3 sebaceous cysts

Epidermal cysts are slow growing, elevated, round, firm, intracutaneous or subcutaneous tumors, varying from 0 2 to 5 cm in diameter They occur most commonly on the scalp As a rule, they are freely movable with the skin No orifice can be demonstrated in the overlying skin The material within them is nearly solid and is odorless

Sebaceous cysts often cannot be differentiated from epidermal cysts on a clinical basis In general, however, sebaceous cysts are softer than epidermal cysts, and, occasionally, they show a small orifice on their surface The material within them is semifluctuant and has a rancid odor

Milia are multiple pinhead sized, whitish, globoid, hard lesions occurring most commonly on the face

Dermoid cysts occur in rare instances in the subcutaneous tissue as soft, round or oval tumors of various sizes The most frequently *observed site is the periorbital region*

Histopathology EPIDERMAL CYSTS have a wall composed of true epidermis, i e , squamous, granular and horn cells (Fig 154) Rete ridges may be present at the periphery of the wall The cyst is filled with keratin which frequently is arranged in laminated layers Foci of calcification are found only in rare instances When the cyst ruptures and the contents of the cyst reaches the dermis, a considerable foreign body *giant cell reaction results The foreign* body reaction may cause breaking up and partial disintegration of the epidermal *cyst*

Malignant degeneration is rare occurring in approximately 1 5 per cent of cases (Love and Montgomery) If such degeneration occurs, it takes the form of squamous cell carcinoma Usually, such carcinomas are of low grade malignancy and do not cause metastases (Peden)

SEBACEOUS CYSTS, or *steatomas*, have a wall composed of epithelial cells that possess no intercellular bridges and do not undergo keratinization. Many of the cells are vacuolated because of their transformation into sebaceous cells (Fig 155). The wall never possesses



FIG 156 Calcified sebaceous cyst. The palisading of the basal layer makes it evident that this is a sebaceous cyst. It has ruptured and fibrous tissue has proliferated into the lumen (×100)

rete ridges at its periphery. The peripheral cell layer shows a distinct palisade arrangement such as is never seen in epidermal cysts. The cysts are filled with amorphous material which forms by the gradual disintegration of the sebaceous cells. Large amounts of cholesterol and cholesterol crystals may be present in the cysts. Calcification occurs frequently within sebaceous cysts (Fig 156). As in epidermal cysts a considerable foreign body reaction results when the wall of a sebaceous cyst ruptures, and the cyst may undergo partial disinte

gration. In rare instances, basal-cell epitheliomas have been found *arising in sebaceous cysts* (Love and Montgomery).

MILIA present a histologic aspect similar to that of epidermal cysts They are, however, much smaller. Milia are not tumors, like the *epidermal and the sebaceous cysts*, but are retention cysts caused by the occlusion of a pilosebaceous follicle (Love and Montgomery)

DERMOID CYSTS are lined by an epidermis endowed with rudimentary *sebaceous glands, sweat glands and hair follicles* They contain sebaceous material as well as keratin. In addition, hairs are present in about 30 per cent of cutaneous dermoid cysts Cartilage and bone are encountered occasionally (New and Erich).

Differential Diagnosis. For differentiation of epidermal and sebaceous cysts and, particularly, of sebaceous cyst with secondary basal cell epithelioma from calcifying epithelioma, see page 368

KERATOSIS SENILIS

Keratosis senilis occurs, frequently as multiple lesions, on the face and the dorsa of the hands in persons past middle life. The lesions



FIG 157 Keratosis senilis. There are hyperkeratosis and papilloma ... tion, are ... shows a rather pronounced chronic inflammatory infiltrate (X100)

usually measure less than 1 cm in diameter and show dry, hard scales firmly adherent to an erythematous base showing little or no infiltration Occasionally lesions of senile keratosis show a verrucous surface In from 20 to 25 per cent of the cases of senile keratosis squamous cell carcinoma develops in one or more of the lesions (Montgomery and Dorffel)

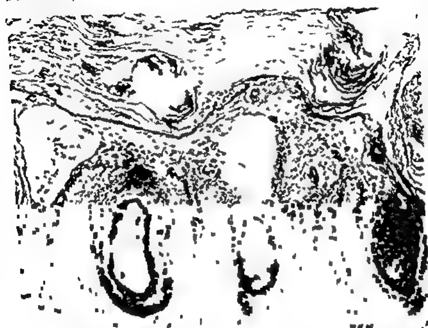


Fig 158 Keratosis senilis *Clefts* and two vesicles are present ... he epidermis ... *in the clefts* ... the dermis as (×150)

Cornu cutaneum a variant of keratosis senilis shows a circumscribed *horny excrescence* sometimes suggesting the horn of an animal

Histopathology The shortest histologic *definition* that may be given to keratosis senilis is that *it represents* a squamous-cell carcinoma Grade ½ It is a *precancerous lesion differing* only in degree from squamous-cell carcinoma or Bowen s disease

Hyperkeratosis is usually pronounced Mild or *moderate* papillomatosis may be present The stratum malpighii varies in thickness ... ay alternate The stratum *of the* rete cells In some ... of cells, individual cell

dyskeratosis, clumping of nuclei and prevalence of mitotic figures are observed, so that the histologic picture approaches that of Bowen's disease (Szodoray) *In other cases, the epidermis* shows irregular downward proliferation but without frank invasion (Fig 157) The histologic picture then approaches that of squamous cell carcinoma Grade I.

Not infrequently, immediately above the basal layer, one observes clefts similar to those seen in Darier's disease (see page 48) These clefts, first described by Freudenthal, may contain a few acantholytic cells In rare instances, even small suprabasal vesicles may be present The basal layer underneath these clefts and vesicles usually consists of cells with large, hyperchromatic nuclei which appear closely set together In addition, this type of atypical basal layer may proliferate *into the dermis as short ductlike structures and, furthermore it may* surround as cell mantles the upper portion of pilosebaceous follicles and sweat ducts the epithelium of which otherwise appears normal (Fig 158) (Halter)

The upper dermis usually shows a fairly dense, chronic, inflammatory infiltrate in which plasma cells are prominent

In instances in which a diagnosis of senile keratosis is made, it often is advisable to section deeper into the block of tissue, because actual progression into squamous cell carcinoma may have taken place in another area

CORNU CUTANEUM is a type of keratosis senilis with particularly pronounced hyperkeratosis

[illegible]

ver

tion of cells of the basal cell type (see page 382) (Freudenthal Montgomery and Dorffel Ruiter) For differentiation from squamous cell carcinoma see page 334 from arsenical keratosis see page 155

LEUKOPLAKIA

Leukoplakia represents senile keratosis of the mucous membranes and occurs on the lips the oral mucosa and the vulva *On the vulva* leukoplakia is apt to develop secondary to senile atrophy of the vulva (see page 162)

Clinically, the lesions consist of white patches which are sharply demarcated, irregular in outline and slightly elevated above the level of the mucous surface The lesions are often multiple and may be discrete or confluent In from 20 to 30 per cent of the cases of leukoplakia squamous cell carcinoma supervenes (MacKee and Cipollaro)

Histopathology. In leukoplakia, hyperkeratosis usually is less pronounced than in keratosis senilis, but the inflammatory infiltrate is

often more intense and may hug the epidermis just as in lichen planus Formation of suprabasal clefts as in senile keratosis does not occur

Differential Diagnosis Differentiation of leukoplakia from lichen planus may be very difficult and occasionally impossible As a rule however the infiltrate in leukoplakia is less severe than in lichen planus and contains a rather large number of plasma cells whereas in lichen planus their number is small In both diseases the epidermal-dermal border is apt to have a hazy outline due to the invasion of the lower epidermis by the inflammatory infiltrate but *only* leukoplakia shows atypicality of the cells in the stratum malpighii On the buccal mucosa pressure of teeth or dentures may produce pressure calluses which show hyperkeratosis acanthosis and a nonspecific inflammatory infiltrate They differ from leukoplakia by the absence of atypicality in the epidermis

SQUAMOUS CELL CARCINOMA (EPIDERMOID CARCINOMA)

Squamous cell carcinoma may occur *anywhere on the skin* as well as on the mucous membranes It may begin as such or develop from a senile keratosis or leukoplakia Most *commonly* the lesion consists of a shallow ulcer surrounded by a wide elevated and *indurated* border The ulcer often is *covered* by a crust which conceals a *red* granular base Occasionally raised fungoid verrucous lesions *without* ulceration occur The latter are usually of a *relatively low grade* of malignancy whereas ulcerated lesions *may grow rapidly* and cause metastases within a short time

Histopathology Squamous-cell carcinoma is a true invasive carci
finds
which
... and invade the *dermis* The invading tumor
masses are composed ...
mous and ...
squamous ...
number of
presses itsel ... as great variation in the size and the shape of the cells *hyperplasia and hyperchromasia* of the nuclei absence of prickles *keratinization of individual cells* prevalence of mitotic figures and presence of *atypical mitotic figures*

Differentiation in *squamous-cell carcinomas* is in the direction of keratinization Keratinization *often takes* place in the form of horn pearls The horn pearls are very ...
of concentric layers of squamous

keratinization toward the center The center may or may not show complete keratinization

Broders introduced a system of grading squamous cell carcinoma He established four grades according to the proportion of differentiated cells to atypical cells In Grade I, more than 75 per cent, in Grade II, more than 50 per cent, in Grade III, more than 25 per cent, and in Grade IV, less than 25 per cent of the cells are differentiated Since differentiation is in the direction of keratinization the degree of keratinization is a good guide in grading Broders system of grading is most useful and has been accepted widely in spite of certain objections raised against it In the first place, there is of course, a large personal factor in the interpretation of cytologic changes, and, secondly, different degrees of malignancy may be present in different fields In regard to the first objection, Broders has suggested to err rather on the side of the higher grade because malignant processes tend to be progressive rather than regressive In regard to the second objection, one should examine several sections of every tumor and grade according to the least differentiated portion (Edmundson)

In squamous cell carcinoma, Grade I (Fig 159), the tumor masses have not penetrated beyond the level of the sweat glands They still show in some areas an intact basal layer at their periphery In other areas the basal layer has become disorganized and has disappeared In such areas the cell masses appear poorly demarcated from the surrounding stroma The cells of the invading cell masses are predominantly mature squamous cells with well developed prickles Nevertheless some of the squamous cells are atypical Horn pearls are present in fairly large number Some are well developed and have fully keratinized centers others, however show only partial keratinization of their centers and the concentric arrangement of the cells is not distinct Besides horn pearls, sheets of partially keratinized cells may be present The dermis often shows a rather marked inflammatory reaction It is noteworthy that, in senile keratosis and squamous cell carcinoma Grade I the inflammatory reaction in the dermis is usually much more pronounced than in the more malignant forms of squamous cell carcinoma This phenomenon is due to the fact that tissue when invaded by carcinomatous cells is able to defend itself to some extent provided the cells are only moderately malignant, but is overwhelmed without any fight if the cells are highly malignant (The same observation incidentally can be made also in malignant melanoma and mycosis fungoides—see pages 460 and 485) Metastases do not as a rule occur as long as a squamous-cell carcinoma remains Grade I

In squamous-cell carcinoma, Grade II (Fig 160), the invading cell masses are, as a rule, poorly demarcated from the surrounding stroma They may invade deeply Keratinization is much less in evidence than in Grade I There are only few horn pearls, and those present show incompletely keratinized centers A fairly large number of the squamous cells are atypical



FIG 159 Squamous-cell carcinoma, Grade I. There is invasion of the dermis by epidermal masses The cells of the invading epidermal masses are predominantly mature squamous cells showing relatively slight atypicality Several horn pearls are present The dermis shows a marked inflammatory reaction (×100)

In squamous-cell carcinoma, Grade III (Fig 161), keratinization is minimal Horn pearls are not found Instead, keratinization occurs *in small cell groups* and *in individual cells* ("individual cell keratinization," "malignant dyskeratosis" see page 499) The majority of cells are atypical Mitotic figures are conspicuous and often atypical.

In squamous-cell carcinoma, Grade IV (Fig 162), keratinization is almost completely absent Nearly all squamous cells are atypical and devoid of prickles Thus, it is often difficult to arrive at the correct

keratinization toward the center. The center may or may not show complete keratinization

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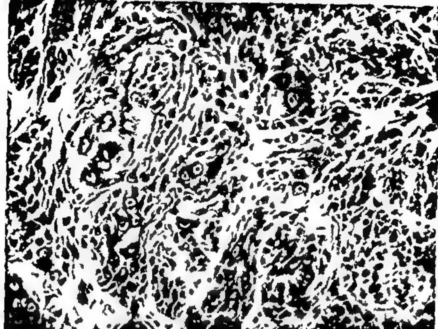


Fig 160 Squamous-cell carcinoma Grade II The cell masses show much less keratinization than in Grade I There are only few horn pearls and those present show incompletely keratinized centers Atypical cells are conspicuous (×200)

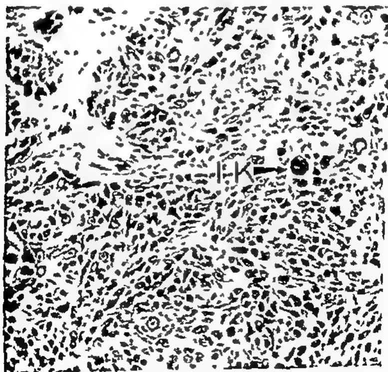


Fig 161 Squamous-cell carcinoma Grade III No horn pearls are present Keratinization occurs only in small cell groups Many cells are atypical and devoid of prickles To the right a cell shows individual cell keratinization (I K) (×200)

diagnosis as long as individual fields only are studied. The tumor may suggest a malignant melanoma in some cases and a sarcoma in others. The latter diagnosis may be particularly difficult to rule out when the cells, as occasionally occurs, are spindle shaped ("spindle-cell" squamous cell carcinoma) (Brooks, Underwood, Montgomery and Broders). If, however, sections are subjected to a thorough study, the type of origin from the epidermis and the presence in a few areas



Fig. 162. Squamous-cell carcinoma, Grade IV. *There is no evidence of keratinization. The epithelial cells appear atypical, are devoid of prickles and elongated so that the tumor suggests a sarcoma almost more than a carcinoma. There are numerous mitotic figures.* (×200)

of cells showing prickles or partial keratinization usually establish the diagnosis. Squamous-cell carcinoma, Grade IV, is relatively rare in the skin. Many of the reported instances of "spindle-cell" squamous-cell carcinoma occurred in areas of radiodermatitis. In this connection, it may be pointed out that it is not yet established fully whether or not sarcomas can develop following radiodermatitis. Most, if not all, cases reported as such in the literature represent squamous cell carcinomas of the spindle-cell type (Sims and Kirsch, Gentele) (see page 122).

Metastases are rare in squamous-cell carcinoma, Grade I, but common in the other grades. The regional lymph nodes are the first site to be invaded by metastases.

Differential Diagnosis. The diagnosis of squamous-cell carcinoma, although easily made in typical cases, may be difficult at times

Squamous cell carcinoma must be differentiated from senile keratosis, pseudo epitheliomatous hyperplasia and basal cell epithelioma

The differences between squamous cell carcinoma and senile keratosis lie in the degree rather than in the type of changes In both conditions, one finds atypicality of cells with dyskeratosis of individual cells and downward proliferation of the epidermis However, in squamous cell carcinoma these changes are more severe, and, in addition, horn pearl formation and actual invasion of the dermis are present No sharp line of separation exists between the two conditions, and it is not infrequent to find in a lesion which in general has the appearance of senile keratosis, on serial sections, one or several areas in which the changes have progressed to squamous cell carcinoma.

For differentiation from pseudo epitheliomatous hyperplasia, see below For differentiation from basal cell epithelioma, see page 380

Pseudo epitheliomatous Hyperplasia

Considerable thickening and irregular proliferation of the skin, which clinically, as well as histologically, may suggest carcinoma, occurs not infrequently in chronic granulomas, such as bromoderma blastomycosis and granuloma inguinale, and at the edges of chronic ulcers, such as occur after burns, in stasis dermatitis, basal cell epithelioma, lupus vulgaris, scrofuloderma, gumma and pyoderma gangrenosum In addition, granular cell myoblastoma is known to evoke quite frequently a pseudo epitheliomatous hyperplasia

Histopathology. Histologically, one observes an epithelial hyperplasia which may closely resemble squamous cell carcinoma, Grades I or II, and therefore is referred to as pseudo-epitheliomatous hyperplasia Although squamous cell carcinoma may develop at the edges of chronic ulcers it is likely that some of the cases that have been regarded as such in the past were in reality pseudo epitheliomatous hyperplasia

The histologic picture of pseudo epitheliomatous hyperplasia shows irregular invasion of the dermis by epidermal cell masses with horn pearl formation and often numerous mitotic figures (Fig 163) The penetration may extend even below the level of the sweat glands as isolated fragments of epidermal tissue (Sommerville) However the squamous cells usually are well differentiated, and atypicalities such as individual cell keratinization and nuclear hyperplasia and hyperchromasia are absent Furthermore in pseudo epitheliomatous hyperplasia, there often are invasion of the epithelial proliferations by leukocytes and disintegration of some of the epidermal cells, a phe

nomenon usually not seen in squamous-cell carcinoma (Winer; Montgomery) But even when all these criteria are taken into account, it may still be difficult to differentiate between squamous cell carci-



FIG 103 Pseudo-epitheliomatous hyperplasia in bromoderma There is *downward* proliferation of the *epidermis analogous* to squamous-cell carcinoma, Grade I In the *field shown it is impossible* to rule out carcinoma Note, however the *permeation* of the epidermis *in many* areas by inflammatory cells (×100)

noma and ...
log
diff

It is worth *remembering* to study *the inflam...*
every section in which one
carcinoma, Grades I or II, f
of the granulomatous *myc...* ... such evidence is found, one may

be dealing with pseudo epitheliomatous hyperplasia rather than with squamous cell *carcinoma*

"Multiple, Primary, Self Healing Squamous Cell Carcinomata"

In this disorder, which often is familial, there is a continuous appearance, especially on the face and the extremities, of papules which grow into nodules, ulcerate and, after a few months, heal with a depressed scar.

Histopathology. The histologic appearance is like that of a well differentiated, keratinizing squamous cell carcinoma, Grade I A dense inflammatory infiltrate is present There may or may not be ulceration, depending on the stage of the lesion

It is generally agreed that differentiation from squamous cell carcinoma is impossible on a histologic basis and depends on the clinical data (Smith, Sommerville and Milne Witten and Zak)

The histogenesis is not clear However, it is certain that the epidermal proliferation represents a pseudo epitheliomatous hyperplasia *Whimster assumes that all the downward prolongations of* epithelium can be explained as extreme hyperplasia, probably inflammatory *in origin, of sweat ducts and hair follicles*

BOWEN S DISEASE

Bowen s disease usually manifests itself as a single lesion It is characterized by a dull red patch of sharp but irregular outline, showing little or no infiltration Within the patch, there usually are areas of crusting beneath which one finds a granular and oozing surface The patch slowly spreads by peripheral extension and shows no tendency to healing in its center

Histopathology. Bowen s disease is an intra epidermal, squamous cell carcinoma, or a squamous cell carcinoma in situ, and not a "pre cancerous dermatosis, under which title it was described *originally* by Bowen

The epidermis *shows hyperkeratosis with parakeratosis* and acanthosis The rete ridges are elongated and thickened, often to such a degree that the papillae *located* between them are reduced to thin strands or are obliterated However, the basal layer is intact, and no true invasion can be seen Throughout the stratum malpighii, the cells lie in complete disorder many are atypical, showing large and hyperchromatic nuclei Multinucleated epidermal cells containing clusters of nuclei are common (Fig 164) Some cells may show marked vacuolization simulating Paget cells However, the intercellular



Fig 164 Bowen's disease The epidermis is thickened the basal layer is intact The cells of the stratum malpighii lie in complete disorder and many of them are atypical showing large and hyperchromatic nuclei Several multinucleated cells with clumped nuclei and numerous mitotic figures are present in the stratum malpighii (×200)

Fig 165 Bowen's disease In addition to the changes, as described for Figure 164 there are within the stratum malpighii three cells showing individual cell keratinization (I K) and one horn pearl (H P) (×200)

bridges of these cells are preserved, in contrast with Paget cells, in which they are absent

A common and if present, characteristic finding is the presence of individual cell keratinization in the stratum malpighii (Fig 165) Such keratinized cells are large and round, have a homogeneous and strongly eosinophilic cytoplasm and a large, irregularly shaped, hyper chromatic nucleus (This individual cell keratinization, which may occur not only in Bowen's disease but also in squamous cell carci noma, is often referred to as malignant dyskeratosis in contrast with the benign dyskeratosis that underlies the formation of corps ronds and grains in Darier s disease) *Occasionally, actual horn pearls may occur within the epidermis*

The upper dermis usually shows a moderate amount of inflam matory infiltration composed chiefly of lymphocytes and plasma cells

As already stated, in true Bowen's disease the basal layer is intact However, in some cases the basal layer ultimately is broken through and a true invasive squamous cell carcinoma results This may occur at first in only one or a few areas In order not to miss such areas it is advisable to examine representative sections throughout the entire tissue block *As soon as the invasion of the dermis occurs, the prog nosis changes* As long as Bowen s disease remains in the true, intra epidermal stage metastases do not occur However, when invasion of the dermis has occurred, the likelihood of metastases is rather great This is due to the fact that if Bowen s disease changes into an in vasive carcinoma, it usually is Grade II or even Grade III with con siderable atypicality of the cells and little tendency to keratinization (Kuznitzky and Jacoby)

Differential Diagnosis. In the differential diagnosis senile kera tosis and arsenical keratosis *must be considered Senile keratosis may* resemble Bowen s disease closely but shows less atypicality of the squamous cells No sharp line of distinction can be drawn between *the two conditions* Arsenical keratosis may closely resemble either Bowen's disease or senile keratosis but shows as a rule, more vacuoli zation of the squamous cells than these two diseases

Erythroplasia of Queyrat

Erythroplasia of Queyrat usually occurs on the glans penis but may be seen *occasionally on the prepuce the vulva or the oral mucosa* The lesion usually single, consists of a well defined area with a bril liant red, velvety surface and little or no infiltration

Histopathology. Erythroplasia represents an intra epithelial squamous cell carcinoma of the mucous membranes and as such is analogous to Bowen's disease of the skin *(Pautrier) Progression into*

invading squamous-cell carcinoma usually occurs sooner than with Bowen's disease of the skin (Sulzberger and Satenstein McDaniel and Mason Pautrier)

Differential Diagnosis Sachs and Sachs as well as Zoon recently have described cases in which the clinical appearance was identical with that of erythroplasia of Queyrat but in which histologic examination revealed no malignant changes in the epidermis Instead the dermis contained an inflammatory infiltrate composed predominantly of plasma cells Zoon has suggested the diagnostic term balanoposthitis chronica circumscripta for these cases Because the two diseases are indistinguishable on clinical grounds it is evident that a diagnosis of erythroplasia of Queyrat always *requires* histologic confirmation

PAGET'S DISEASE

Paget's disease of the nipple occurs as a rule on and around the nipples of women a few instances of its occurrence on the male breast have been described (Rubenstein) The lesion is always unilateral Extramammary Paget's disease which is uncommon occurs on or near the male and the female genitals in the perianal region and in the axillae

The lesion of Paget's disease consists of a sharply defined slightly infiltrated area of dusky erythema showing scaling oozing and crusting If located on the breast the process begins in the nipple or the areola of the breast and slowly extends to the surrounding skin There may or may not be retraction of the nipple

Histopathology For many years Paget's disease of the nipple was thought to begin in the skin as a precancerous lesion that later became malignant and then invaded the mammary gland It is now generally accepted that Paget's disease of the nipple is a cancer from the outset and that the initial lesion is a carcinoma in situ arising in one or more mammary ducts near their outlets The primary duct cancer extends from the site of origin downward to the epithelium lining the acini and upward and outward to the epidermis where it causes the cutaneous lesion Thus the tumor cells present in the epidermis often referred to as Paget cells are ductal and not epidermal cells (Pautrier Fraser Muir Inglis) At a later stage the cancer breaks through the wall of a duct or acinus and infiltrates the connective tissue of the breast

A carcinoma has been found in the mammary ducts in nearly all cases of Paget's disease and in the mammary glands in most cases In the few cases where no carcinoma was found in the breast the underlying ductal carcinoma may have been overlooked because in the

bridges of these cells are preserved, in contrast with Paget cells, in which they are absent

A common and, if present, characteristic finding is the presence of individual cell keratinization in the stratum malpighii (Fig 165) Such keratinized cells are large and round, have a homogeneous and strongly eosinophilic cytoplasm and a large, irregularly shaped, hyperchromatic nucleus (This individual cell keratinization, which may occur not only in Bowen's disease but also in squamous cell carcinoma, is often referred to as malignant dyskeratosis in contrast with the benign dyskeratosis that underlies the formation of corps ronds and grains in Darier's disease) Occasionally, actual horn pearls may occur within the epidermis

The upper dermis usually shows a moderate amount of inflammatory infiltration composed chiefly of lymphocytes and plasma cells

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Differential Diagnosis. In the differential diagnosis, senile keratosis and arsenical keratosis must be considered Senile keratosis may resemble Bowen's disease closely but shows less atypicality of the squamous cells No sharp line of distinction can be drawn between the two conditions Arsenical keratosis may closely resemble either Bowen's disease or senile keratosis but shows, as a rule more vacuolization of the squamous cells than these two diseases

Erythroplasia of Queyrat

Erythroplasia of Queyrat usually occurs on the glans penis but may be seen occasionally on the prepuce the vulva or the oral mucosa The lesion usually single consists of a well defined area with a brilliant red, velvety surface and little or no infiltration

Histopathology. Erythroplasia represents an intra epithelial squamous cell carcinoma of the mucous membranes and as such is analogous to Bowen's disease of the skin (Pautrier) Progression into



Only a
re large



FIG. 168 Paget's disease of the nipple. Intraductal carcinoma is present in the mammary ducts. The carcinoma is confined within the walls of the ducts (×200)

ducts the carcinoma may undergo considerable regression with resultant sclerosis and calcification of the involved ducts (Marx)

Histologic examination of the epidermis reveals in early lesions acanthosis with elongation of the rete ridges, and in older lesions

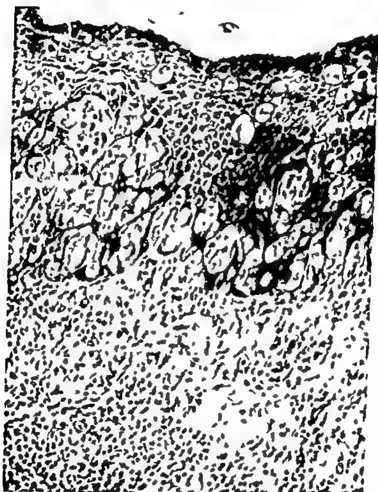


Fig 166 Paget's disease of the nipple Low magnification The epidermis is permeated with numerous Paget cells lying singly and in groups Note that there is no invasion of the dermis by Paget cells An inflammatory infiltrate is present in the dermis (×200)

thinning and flattening Paget cells are scattered through the epidermis (Fig 166) They are large, devoid of prickles and at times appear to lie in clear spaces (Fig 167) Their cytoplasm stains much lighter than that of the adjacent squamous cells Their nuclei are large, round and pale staining Paget cells usually are most numerous in the basal layer and may cause disorganization of this layer Invasion of the dermis from the epidermis however, does not occur

2 TUMORS OF THE EPIDERMAL APPENDAGES

NEVUS SEBACEUS (JADASSOHN)

Nevus sebaceus is located most commonly on the scalp or on the face as a single lesion present since birth. It consists of a circum-



Fig 169 Nevus sebaceus (Jadassohn) There are hyperkeratosis and papillomatosis Numerous mature sebaceous glands lie in the upper dermis In the lower dermis mature apocrine glands are located (X50)

scribed slightly raised firm yellow plaque with a smooth though furrowed surface

Histopathology The tumor is composed of large numbers of mature or nearly mature sebaceous glands The overlying epidermis may or – . Frequently apo
crı … n nevus sebaceus
(R … ep in the dermis
beneath the masses of sebaceous gland lobules (Fig 169) The presence of abortive hair follicles has also been noted on several occasions

In some cases, Paget cells are so numerous throughout the epidermis that the normal squamous cells show signs of injury. They are compressed and deformed and may form only a network, the meshes of which are filled with Paget cells (Fig 166)

The dermis shows in Paget's disease a moderately severe chronic inflammatory reaction

Histologic examination of the mammary ducts nearly always shows malignant changes in some of them At first, the carcinoma is intraductal and the tumor cells are confined within the walls of the ducts (so called comedo carcinoma) (Fig 168) Ultimately, the tumor cells invade the connective tissue. From then on, lymphatic spread and metastases occur.

EXTRAMAMMARY PAGET'S DISEASE, as a rule, presents the same epidermal changes as Paget's disease of the nipple, although in lesions located in the perianal region the Paget cells often contain a considerable amount of mucin In most reported cases, an underlying carcinoma of apocrine ducts and glands has been found (Parsons, Foraker and Miller, Zoon and Gelpke) This is in accordance with the fact that the mammary gland is a modified apocrine gland The presence of mucin within the Paget cells of some of the cases located in the perianal region may be the result of mucous metaplasia of apocrine glands, but Whimster suggests that the primary cancer may be one of ectopic mucous glands rather than of apocrine glands

Differential Diagnosis. *Paget's disease of the nipple* must be differentiated from Bowen's disease In Bowen's disease, large, vacuolated epidermal cells may also occur, but, in contrast with the Paget cells, they often possess prickles Furthermore, one observes clumping of nuclei within multinucleated epithelial giant cells and individual cell keratinization in Bowen's disease but never in Paget's disease In cases in which the Paget cells are concentrated in the lower epidermis, the resemblance to an amelanotic junction nevus or an early malignant melanoma may be very great because in both diseases the characteristic cell is large and vacuolated (Stout) Allen believes that many cases of Paget's disease and especially of extramammary Paget's disease are wrongly thus diagnosed and in reality are junction nevi The most important points of differentiation are first, the absence of invasion of the dermis by the tumor cells in Paget's disease, and second, the presence of minute amounts of melanin in at least some tumor cells even in apparently amelanotic junction nevi and malignant melanomas The melanin is best demonstrated by the use of a silver stain Carrying out of the dopa stain (see page 12) also aids in the differentiation

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Histopathology The tumor
ture or nearly mature sebaceous
or may not show hyperkeratosis
crine glands have been descr... occurring in nevus sebaceus (Robinson Koch Pautrier) They are located deep in the dermis beneath the masses of sebaceous gland lobules (Fig 169) The presence of abortive hair follicles has also been noted on several occasions

(Ostrowski). Koch and Pautrier believe that the frequent presence of apocrine glands is evidence that nevus sebaceus develops from primary epithelial germs (For a discussion of the primary epithelial germ, see pages 4 and 318.)

The presence of a basal cell epithelioma within a nevus sebaceus is not uncommon (Fig. 170) (Ostrowski; Robinson; *Szodoray*, Pautrier,



FIG. 170 Nevus sebaceus (Jadassohn) within which a basal cell epithelioma has arisen The nevus sebaceus is on the right side, the basal cell epithelioma on the left (×25)

Savatard) In rare instances, a squamous-cell carcinoma may develop from the epidermis overlying the nevus sebaceus (Parkin).

ADENOMA SEBACEUM (PRINGLE) (TUBEROUS SCLEROSIS)

Adenoma sebaceum (Pringle) usually represents only part of a widely disseminated tissue malformation which results in the formation of tumors in both ectodermic and mesodermic structures Tumors are found, aside from the skin, notably in the brain, the retina, the kidney and the heart The tumors in the brain, which are referred to as tuberous sclerosis, are gliomas Those of the retina have the same *histologic appearance* as the brain tumors (Kvem) The tumors of the heart usually are rhabdomyomas (Pratt-Thomas). Those of the kidney may be angiomas, fibromas, adenomas or mixed tumors; they may become malignant (Butterworth and Wilson).

The cutaneous lesions of adenoma sebaceum (Pringle) occur on the face, particularly in the malar region They consist of numerous small papules and nodules which are yellowish brown in color and frequently show telangiectases on their surface

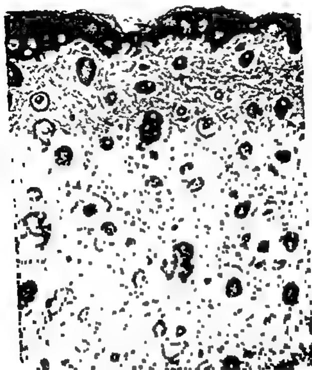


FIG 171 Adenoma sebaceum (Pringle). Instead of showing excessive development of sebaceous glands, as is usually the case, this lesion shows a large number of immature hair structures (×50)

Histopathology. The term adenoma sebaceum is a misnomer Since the sebaceous structures are not adenomatous but fully or almost fully developed and abnormal merely by their presence in excessive number, the lesion represents an organic nevus, rather than an adenoma (see Table C [illegible]

In addition to [illegible]
find [illegible]

[illegible] a large number of hair structures are found Usually, those hair structures are somewhat immature (Fig 171) (Butterworth and Wilson, Good and Garb)

(Ostrowski). Koch and Pautrier believe that the frequent presence of apocrine glands is evidence that nevus sebaceus develops from primary epithelial germs. (For a discussion of the primary epithelial germ, see pages 4 and 318.)

The presence of a basal-cell epithelioma within a nevus sebaceus is not uncommon (Fig. 170) (Ostrowski; Robinson; Szodoray, Pautrier;



FIG 170. Nevus sebaceus (Jadassohn) within which a basal cell epithelioma has arisen The nevus sebaceus is on the right side, the basal cell epithelioma on the left (×25)

Savatard) In rare instances, a squamous cell carcinoma may develop from the epidermis overlying the nevus sebaceus (Parkin).

ADENOMA SEBACEUM (PRINGLE) (TUBEROUS SCLEROSIS)

Adenoma sebaceum (Pringle) usually represents only part of a widely disseminated tissue malformation which results in the formation of tumors in both ectodermic and mesodermic structures Tumors are found, aside from the skin, notably in the brain, the retina, the kidney and the heart The tumors in the brain, which are referred to as tuberous sclerosis, are gliomas Those of the retina have the same histologic appearance as the brain tumors (Kverm). The tumors of the heart usually are rhabdomyomas (Pratt-Thomas) Those of the kidney may be angiomas, fibromas, adenomas or mixed tumors; they may become malignant (Butterworth and Wilson)

SEBACEOUS ADENOMA

An adenoma may be defined as an organoid tumor consisting of circumscribed proliferations of incompletely differentiated glandular structures If this definition is adhered to, sebaceous adenoma is a very rare tumor Many tumors described in the literature as sebaceous



FIG 172 Sebaceous adenoma The tumor is composed of lobules which are irregular in size and shape Two types of cells compose the lobules, generative and sebaceous cells (×100)

adenoma are in reality sebaceous nevi Examples of sebaceous adenoma have been described by Reitmann, Pautrier, Woolhandler and Becker, and Lever, among others

Sebaceous adenoma occurs as a smooth, firm, round, elevated, often slightly pedunculated, tumor In most reported cases, the lesion was solitary, located on the face or the scalp, and measured less than 1 cm in diameter

Histopathology. On histologic examination, the tumor is sharply demarcated from the surrounding tissue and is usually surrounded by a connective tissue capsule It is composed of lobules which are irregular in size and shape (Fig 172) Two types of cells are present

SENILE SEBACEOUS NEVUS (SENILE SEBACEOUS HYPERPLASIA)

Senile sebaceous nevus occurs on the face, chiefly on the forehead, in persons past middle life, and consists of either one or a few small yellowish, translucent nodules

Histopathology. This lesion, like nevus sebaceus (Jadassohn) and adenoma sebaceum (Pringle), is composed of large numbers of mature or nearly mature sebaceous glands Differentiation of senile sebaceous nevus from the other two lesions on histologic grounds is therefore, often impossible In contrast with nevus sebaceus and adenoma sebaceum (Pringle), however, apocrine glands or immature hair follicles are never found

Senile sebaceous nevus is regarded by some writers as a senile hyperplasia of sebaceous glands (Gilman, Woolhandler and Becker), while others consider it as a delayed, senile organic nevus or hamartoma (Gans) The circumscribed nature of the lesions makes the latter view more likely than the former

FORDYCE'S DISEASE

In this condition, groups of minute, yellowish, globoid lesions are observed on the vermilion border of the lips or on the oral mucosa

Histopathology. Fordyce's disease has as pathologic substrate the presence of sebaceous glands in areas where they are normally absent It thus represents a sebaceous nevus or hamartoma

Histologic examination reveals groups of mature sebaceous lobules located in the upper dermis Some lobules lie free in the dermis others lie at the end of downward proliferations of the overlying epidermis, and still others are connected with the epidermis by true sebaceous ducts (Chambers) However, hairs are never found

APOCRINE GLAND NEVUS

Organic nevi composed only of apocrine glands *do not occur* Apocrine gland structures however, frequently are present in nevus sebaceus (Jadassohn) (see page 343) and occasionally in nevus verrucosus (see page 322)

HAIR NEVUS

Purely hair nevi occur, but *more commonly they appear in con*junction with other nevoid lesions, for instance with nevus sebaceus (Jadassohn), nevus verrucosus and nevus pigmentosus Some cases of adenoma sebaceum (Pringle) are *hair nevi rather than sebaceous nevi* (see page 345)

sebaceous lobules In most lobules, however, the two types of cells occur in approximately equal proportions, often arranged in such a way that groups of sebaceous cells are surrounded by generative cells Larger lobules may contain in their center cystic spaces formed by the decomposition of mature sebaceous cells

Fat stains reveal the presence of fat in the sebaceous and transitional cells and in the cystic spaces

SYRINGOCYSTADENOMA PAPILLIFERUM (NEVUS SYRINGOCYSTADENOMATOSUS PAPILLIFERUS)

This tumor represents an apocrine gland adenoma with differentiation predominantly toward apocrine ducts in contrast with hidradenoma papilliferum in which differentiation is directed predominantly toward apocrine glands



Fig 174 Syringocystadenoma papilliferum. High magnification of Figure 173 The villi are lined by two rows of cells The outer row is composed of small cuboidal cells (myo-epithelial cells) the inner row of high cylindrical cells (secretory cells of apocrine glands) (×200)

Clinically, syringocystadenoma papilliferum occurs usually ... single verr... tered th... cysts can

in the lobules The cells of the first type are identical with the cells present at the periphery of normal sebaceous glands and resemble the cells of which basal cell epitheliomas are composed They have



*Fig 173 Syringocystadenoma papilliferum Low mag*nification A cystic invagination extends downward from the epidermis Numerous villuslike projections extend into *the lumen* of the cystic invagination A group of apocrine glands (A P) is present in the left lower corner (×50)

been called generative cells by Grynfeltt (see page 17) The cells of the second type are mature sebaceous cells They have developed from the generative cells In addition there are cells in a transitional stage of differentiation The distribution of the generative and the sebaceous cells *within the lobules* varies *Some* lobules contain predominantly generative cells and thus resemble basal cell epithelioma Other lobules contain mainly sebaceous cells and resemble mature

ence of active secretion These cells represent secretory cells Cel ular debris is found in the lumina

Beneath the cystic invaginations deep in the dermis one finds groups of glandular lumens (Fig 175) Their secretory activity (de capitation secretion) clearly labels them as apocrine glands (Fig 176) (Tappeiner Appel Grund) Connections of the apocrine glands



Fig 176 Syringocystadenoma papilliferum High magnification of the apocrine glands in Figure 175 The secretory cells of the apocrine glands show evidence of active secretion (decapitation secretion) (×400)

with the cystic invaginations in the upper dermis can be traced without difficulty

In most cases a dense inflammatory infiltrate is present in the upper dermis and especially in the villi This infiltrate contains a large percentage of plasma cells and in some cases is composed almost exclusively of plasma cells

The association of syringocystadenoma papilliferum with nevus sebaceus (Dorffel Marcus and Wooldridge Grund) or with basal cell epithelioma (Dorffel Reuterwall) has been noted on several occasions

Differential Diagnosis For differentiation from Darier s disease in which villi are also sometimes very *prominent*, see page 50

Histopathology. The epidermis shows acanthosis and papillomatosis. Cystic invaginations extend downward from the epidermis (Fig 173). These invaginations represent greatly dilated apocrine ducts



Fig. 173 Syringocystadenoma papilliferum. Low magnification In the upper dermis there are several cystic invaginations filled with villuslike projections A marked inflammatory infiltrate containing many plasma cells is present around the cystic invaginations The lower dermis contains numerous apocrine glands (×50)

Numerous villuslike projections extend into the lumina of the invaginations The cystic invaginations, as well as the villi, are lined by two rows of cells (Fig 174) The outer row is composed of small cuboidal cells with deeply staining nuclei These cells are immature myo epithelial cells. The inner row is composed of high, cylindrical cells which have large, oval, pale-staining nuclei and may show evi

larly



Gates Warren and Warvi have pointed out that hidradenoma papilliferum closely resembles the papillary cystadenomas of the mammary gland It should be remembered that, phylogenetically, the mammary gland is an apocrine gland

SEBACEOUS EPITHELIOMA

Clinically the tumor has no characteristic appearance Usually, it presents itself as a solitary small nodule or plaque It is an uncommon type of tumor Examples have been described by Grynfeltt, Biberstein Milian, Perin and Brunel, and Lever

Histopathology. In degree of differentiation sebaceous epithelioma stands between sebaceous adenoma in which there are typical sebaceous lobules, and cystic basal-cell epithelioma, in which there

HIDRADENOMA PAPILLIFERUM

This tumor occurs almost exclusively on the labia majora and on the perineum of women as a solitary intracutaneous lesion covered by normal epidermis It usually measures only a few millimeters in diameter Malignant degeneration does not occur



FIG 177 Hidradenoma papilliferum Low magnification The tumor consists of a large cystlike lumen into which numerous interlacing villi project (×50)

Histopathology The tumor represents an adenoma of apocrine glands (Anderson Winer) It is located in the dermis shows no connection with the epidermis and is well encapsulated It is composed of a large cystlike lumen into which numerous interlacing villi project (Fig 177) The wall of the cyst as well as the villi are lined usually by a single layer of high cylindrical cells These cells have a

differentiation is directed mainly toward apocrine duct cells, differentiation in cylindroma is directed mainly toward apocrine gland cells and in myo epithelioma mainly toward apocrine myo epithelial cells

... in women and develops at ... yellowish nodules, the size

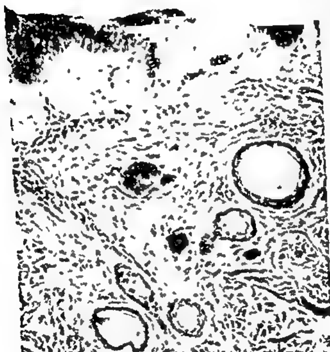


Fig 180 Syringoma The dermis contains several small cystic ducts The walls of most ducts are lined by two rows of epithelial cells Colloidal material fills the lumina Two of the ducts have comma like tails giving them the appearance of tadpoles (×200)

of a pinhead are found around the eyelids on the chest, on the abdomen and on the anterior aspects of the thighs, but occasionally also elsewhere on the skin

Histopathology The dermis contains numerous, small, cystic ducts (Fig 180) The walls of the ducts are lined usually by two rows of epithelial cells In most instances these cells are flat and ... if compressed ... evidence of act

is but little differentiation toward sebaceous cells (See Table 6 page 319) As Loos has put it sebaceous epithelioma grows like a basal cell epithelioma but its cells have undergone considerable differentiation toward sebaceous cells

The tumor is composed of irregularly shaped cell masses which are scattered through the upper dermis (Fig 179) The majority of cells



Fig 179 Sebaceous epithelioma The tumor is composed of irregularly shaped cell masses The majority of cells are of the same type as in basal-cell epithelioma but many cells (SC) show differentiation toward sebaceous cells (×100)

are of the same type as the cells in basal cell epithelioma However a fairly large number are transitional cells showing beginning fatty transformation of their cytoplasm Groups of mature sebaceous cells lie in the centers of the cell masses Cysts formed by the disintegration of sebaceous cells may or may not be present in the center of some of the tumor masses

SYRINGOMA

Three types of apocrine epitheliomas occur syringoma cylindroma and myoepithelioma (see Table 6) While in syringoma

Besancon Riehl Homma and Fscher Wendlberger) (2) its simultaneous occurrence with rudimentary hair structures or with trichoepithelioma a tumor of hair structures (Fischer Lever) (3) its appearance at puberty when apocrine glands first begin to function (Kyrle Wendlberger) and (4) the prevalence of the lesions in areas of the skin where apocrine glands occur or used to occur phylogenetically (Wendlberger)

CYLINDROMA

This disorder which is often hereditary is characterized by the presence of numerous rounded smooth tumors of various sizes on



F... 81 Two ... nes ... apocr ne gland cells (X?00)

the scalp Occasionally a few tumors are present also on the face and the upper trunk The lesions begin to appear in early adulthood and increase in number and size throughout life They vary in siz from a few millimeters to several centimeters and by their arrangement in groups resemble bunches of grapes or tomatoes The tumor

man and Besancon; Riehl; Homma and Escher; Wendlberger). The lumina of the ducts are filled with a colloidal material Some of the cystic ducts possess small, comma-like tails of epithelial cells, giving them the appearance of tadpoles In addition, there are solid strands of epithelial cells independent of the ducts. The cells composing the

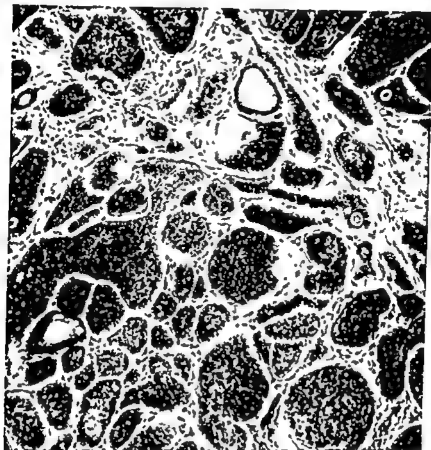


Fig. 181 Cylindroma. Low magnification The tumor is composed of various sized islands of epithelial cells The islands are surrounded by a hyaline membrane Several of the islands in the left lower quadrant contain droplets of hyalin (×75)

solid strands have the same appearance as the cells in basal cell epithelioma. Rudimentary hair structures are found occasionally in the lesions (*Fischer*).

Several authors have reported the simultaneous occurrence of syringoma and tricho epithelioma (epithelioma adenoides cysticum) in the same patient (*McDonagh; Weidman and Besancon*) and even *in* the same lesion (Ingels; Lever).

The reasons given by various authors for the apocrine genesis of syringoma are: (1) the presence of active secretion (*Weidman and*

Besancon Riehl Homma and Escher Wendlberger) (2) its simultaneous occurrence with rudimentary hair structures or with trichoepithelioma a tumor of hair structures (Fischer Lever) (3) its appearance at puberty when apocrine glands first begin to function (Kyrle Wendlberger) and (4) the prevalence of the lesions in areas of the skin where apocrine glands occur or used to occur phylogenetically (Wendlberger)

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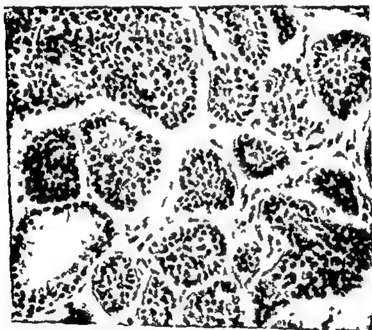


Fig 18? Cylindroma H gh magn ficat on of F g re 181 ?r

s of the inner row show active secret on like apocrine gland cells (×?00)

the scalp Occasionally a few tumors are present also on the face and the upper trunk The lesions begin to appear in early adulthood and increase in number and size throughout life They vary in size from a few millimeters to several centimeters and by their arrangement in groups resemble bunches of grapes or tomatoes The tumors

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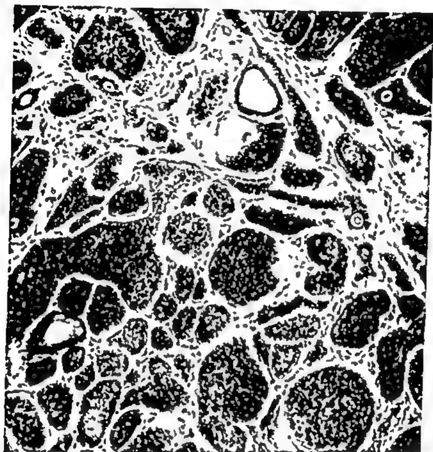


FIG 181 Cylindroma Low magnification The tumor is composed of various sized islands of epithelial cells The islands are sur
lower quadrant contain droplets of hyalin (×75)
rounded by a hyaline membrane Several of the islands in the left

solid strands have the same appearance as the cells in basal cell epithelioma Rudimentary hair structures are found occasionally in the lesions (Fischer)

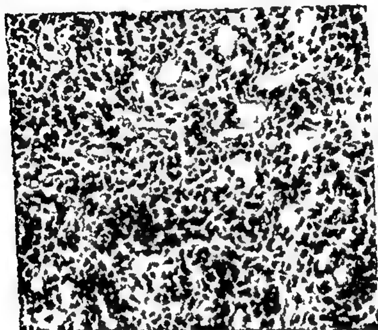
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nd (3) its simultaneous occurrence with tricho epithelioma a tumor of hair structures

MYO EPITHELIOMA (MYO EPITHELIAL SWEAT GLAND TUMOR)

Myo epithelioma occurs as a rule as a solitary tumor occasionally however several lesions are present The tumors present themselves



as firm intracutaneous *nodules and usually* measure between 0 5 and 2 cm in diameter although *they may be larger* The overlying skin is either normal or shows *slight erythema* Myo-epithelioma is a rather uncommon tumor *Examples have been* described by Sheldon Balog, Hartz and Lever

Histopathology *Histologic* examination reveals a sharply circum scribed usually *encapsulated* essentially *solid* tumor The epithelial cells of the tumor are arranged *usually in* intertwining bands but occasionally in lobular masses. *The same* two types of cells are pres ent as in cylindroma namely *secretory* and myo-epithelial cells but

may cover the entire scalp like a turban For this reason, they are referred to occasionally as turban tumors

Histopathology. *The tumors are composed of numerous, variously sized islands of epithelial cells* These islands are surrounded by a hyaline membrane In addition, droplets of hyalin are present in some of the islands (Fig 181) Two types of cells compose the islands (Stillians, Savatard, Zakon, Lever) Cells with large, oval, light staining nuclei lie in the centers of the islands, while cells with small, round, dark staining nuclei are present in palisade arrangement at the periphery of the islands and also scattered between the cells of the first type (Fig 182) The cells of the first type may be regarded as cells differentiating toward secretory cells, those of the second type as cells differentiating toward myo epithelial cells of apocrine glands The secretory cells always outnumber the myo epithelial cells The hyalin which is present around and within the islands appears to be produced by the myo epithelial cells, since it is always found in apposition to them It is particularly well demonstrated by staining with methylene blue

In some cases, a thorough inspection of the histologic sections will reveal the presence of a few glandular lumina lined by two layers of cells an inner actively secreting layer and an outer myo epithelial layer (Stillians, Lever) (Fig 182) These glandular structures strongly resemble apocrine glands

Several authors have observed connections of the tumor masses with hair follicles (Watanabe, Stillians Schlammadinger) The simultaneous presence of cylindroma and tricho epithelioma (epithelioma adenoides cysticum) in the same patient has been observed repeatedly (Watanabe Schlammadinger Schuermann and Weber, Savatard) Cylindromas nearly always remain benign Two cases however, are on record in which malignant degeneration of the tumors occurred with metastases to the lymph nodes in one case (Lausecker) and to internal organs as well in the other (Luger) The areas of malignant degeneration showed in the cell lobules polymorphism of the nuclei numerous mitotic figures loss of the hyaline sheath, loss of palisading at the periphery and invasion into the surrounding stroma

The histogenesis of cylindroma is not yet clearly established Some authors (Coenen, Davies) regard it as a sweat gland tumor, others (Watanabe, Stillians, Schlammadinger) as a hair follicle tumor and still others (Balog Schuermann and Weber) as an apocrine tumor In favor of the apocrine genesis of cylindroma are (1) the presence of two types of cells namely, secretory and myo epithelial cells (2) the occasional presence of actively secreting glandular lumina

and (3) its simultaneous occurrence with tricho-epithelioma, a tumor of hair structures

MYO EPITHELIOMA (MYO EPITHELIAL SWEAT GLAND TUMOR)

Myo epithelioma occurs as a rule as a solitary tumor occasionally, however several lesions are present The tumors present themselves

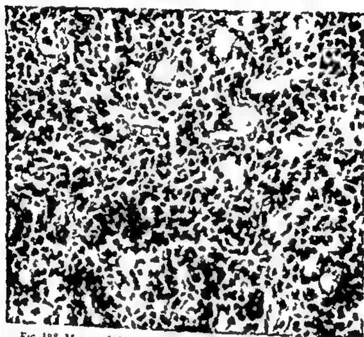


Fig 183 Myo-epithelioma The epithelial cells are arranged in intertwining bands *Two types of cells can be seen* Secretory cells lie in the center of the bands and tend *to be* arranged around lumina Myo-epithelial cells lie at the periphery of the bands (X400)

is 5 cm

Histopathology *Histologic* examination *reveals* a sharply circumscribed usually encapsulated essentially solid tumor The epithelial cells of the tumor are arranged *usually* in intertwining bands but occasionally in lobular masses *The same* two types of cells are present as in cylindroma namely secretory and myo epithelial cells, h

in contrast with cylindroma, the majority of cells are myo epithelial cells The secretory cells lie in groups and frequently are arranged around lumina which are usually small

In myo epitheliomas with bandlike arrangement of the epithelial cells, the secretory cells are located in the center and the myo epi

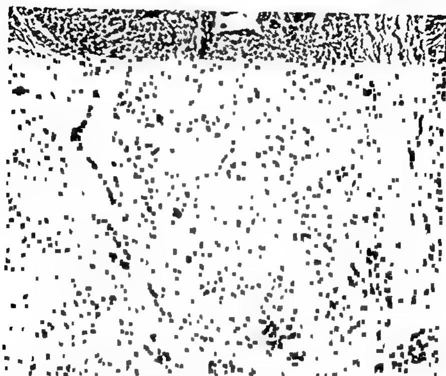


Fig 184 Myo-epithelioma The epithelial cells are arranged in lobules The lobule shown is composed largely of myo epithelial cells but lumina lined with secretory cells are scattered through the lobule (×200)

thelial cells at the periphery of either tubules or solid bands (Fig 183) The myo epithelial cells may be seen proliferating irregularly into the stroma In myo epitheliomas with lobular arrangement, the lobules are composed largely of myo epithelial cells, but throughout the lobules one finds lumina lined with secretory cells (Fig 184)

Some of the tumors possess a considerable amount of stroma of hyaline appearance and thus resemble the so called mixed tumors of the salivary gland type

Mixed Tumor of the Skin

Mixed tumors of the salivary gland type occasionally have been described as occurring in the skin (Hirsch, Highman, Morehead,

Lennox Pearse and Richards) Their clinical appearance is the same as that of myo epithelioma

Histopathology Mixed tumors of the skin show epithelial cells arranged in nests and strands as well as around small lumina (Fig 185) Either one or two layers of epithelial cells are present around the lumina In addition epithelial cells may be seen proliferating irregularly from the lumina into the stroma The majority of epithelial cells are spindle shaped and resemble myo-epithelial cells (Morehead) Those located around lumina have the appearance of glandular cells The stroma usually is abundant and shows hyaline and mucoid degeneration

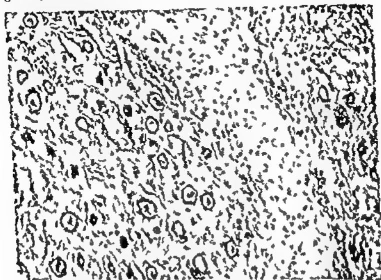


Fig 185 Mixed tumor of the skin Epithelial cells lie arranged around small tubular lumina and scattered through the stroma The stroma shows mucoid and hyaline degeneration (×100)

Some authors regard the mixed tumors of the skin as of sweat gland origin (Hirsch Lennox Pearse and Richards) It is the author s belief that most if not all mixed tumors of the skin represent myo epitheliomas They differ from myo epitheliomas only by showing a greater amount of stroma and more marked degenerative changes in the stroma.

Clear Cell Myo epithelioma

The clinical appearance of this tumor is that of a solitary nodule usually covered by intact skin but occasionally discharging serous material

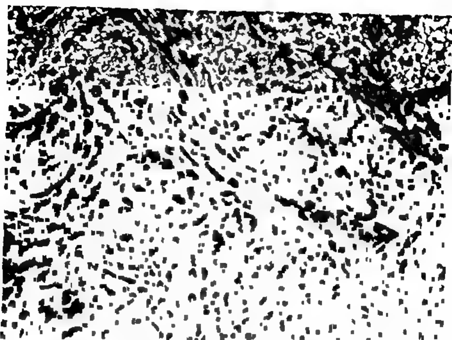


FIG 186 Clear cell myo epithelioma The tumor is composed of two types of cells fusiform myo epithelial cells and cuboidal "clear cells" (×200)



FIG 187 Clear-cell myo epithelioma There are numerous clear cells and in addition, tubular lumina lined by a single layer of secretory cells (×200)

Histopathology The tumor has a lobular structure Two types of epithelial cells can be recognized fusiform myo epithelial cells with deeply basophilic nuclei and clear cells which are cuboidal have a distinct cellular membrane very clear cytoplasm and a round nucleus (Fig 186) The clear cells seem to develop from the myo epithelial cells (Lever and Castleman) Varying amounts of glycogen are present in the clear cells In some tumors there are groups of keratinized cells cysts and glandular structures The glandular structures are tubular and their lining cells often show decapitation secretion as observed in apocrine glands (Fig 187)

While Lever and Castleman regard this type of tumor as a variant of myo epithelioma Liu because of the presence of glycogen thought that it was derived from the outer hair sheath which normally contains abundant amounts of glycogen However glycogen is found so commonly in young cells and in tumors that its presence cannot be considered as a reliable criterion for the histogenetic classification of neoplasms

TRICHO EPITHELIOMA (EPITHELIOMA ADENOIDES CYSTICUM MULTIPLE BENIGN CYSTIC EPITHELIOMA)

The name tricho epithelioma is preferable to the other names listed above because it indicates that differentiation in this tumor is directed toward hair structures

The disorder begins as a rule at the age of puberty and is frequently hereditary It is characterized by the presence of numerous pinhead to pea sized rounded yellowish or pink nodules on the face and occasionally on the upper trunk A few telangiectatic vessels are often present on the surface of the larger lesions Occasionally one or several lesions become ulcerated because of change into a basal-cell epithelioma

Histopathology On histologic examination tricho epithelioma appears as a well-circumscribed tumor Horn cysts represent the characteristic lesion They consist of a fully keratinized center surrounded by a shell of flattened basal cells without prickles (Fig 188) The keratinization in the horn cysts is abrupt and complete not gradual and incomplete as in the horn pearls of squamous-cell carcinoma This process corresponds to the abrupt development of the horn cells of the hair from the hair matrix cells (which are also cells without prickles) It may be concluded therefore that the cells surrounding the horn cysts are hair matrix cells and that the horn cysts represent attempts at hair shaft formation (Lever) Occasionally one sees prickle cells around some of the horn cysts They represent outer hair sheath cells Since the outer hair sheath develops from

prickle cells at a time when the hair germ has already advanced to a rather high stage of differentiation the presence of prickle cells around the horn cysts is evidence of rather high differentiation

In addition to horn cysts irregularly shaped islands and intertwining strands composed of basal cells are present Such areas are indistinguishable from basal-cell epithelioma (Goldman) Abortive



FIG 188 Trichoepithelioma The tumor contains numerous horn cysts In the center near the epidermis two rudimentary hairs can be seen (×100)

hair papillae and hair shafts are seen occasionally Since hair papillae contain a high concentration of alkaline phosphatase (Hardy) their presence can be well demonstrated by the use of the Gomory stain for alkaline phosphatase Calcification of the horn cysts may occur and evoke a foreign body giant cell reaction in the adjacent connective tissue

Tumors histologically in an intermediate stage between trichoepithelioma and basal cell epithelioma occur (Summerill and Hutton Traenkle) As just stated a typical trichoepithelioma is characterized by circumscribed growth and by the presence of many horn cysts and of basal cell masses however basal cell epithelioma may

also show horn cysts (Fig. 189) (see page 379) and may be circumscribed in growth. Since thus no sharp line of demarcation exists between tricho-epithelioma and basal-cell epithelioma histologically, it may be necessary, in order to arrive at a diagnosis in a given case, to have knowledge of clinical data, such as the number and the distribution of the lesions and the age at which the lesions first ap-

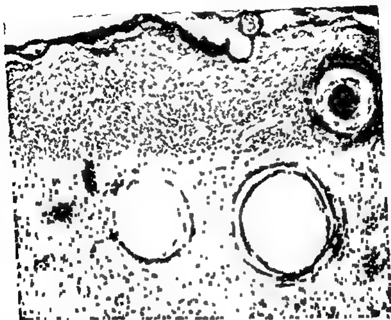


Fig. 187. Basal-cell epithelioma with horn cysts. Histologically, this tumor is in an intermediate stage of differentiation between basal cell epithelioma and tricho-epithelioma. Clinically, the lesion was a basal cell epithelioma. (×200)

peared. The close relation between the two types of tumors is attested further by reports of cases in which one or several of the lesions of tricho-epithelioma, after having persisted as such for many years, developed into ulcers with the histologic picture of basal cell epithelioma (Adamson, Little, Savatard). This close relationship of the two types of tumors can be explained best by assuming that they have a common genesis from primary epithelial germs (Lever) and that they differ only in the degree of maturity of their cells (Adamson). Since cells of various maturity may occur in the same lesion, one may find in tricho-epithelioma areas consistent with the histologic picture of basal-cell epithelioma and vice versa; also, if active growth occurs in a lesion of tricho-epithelioma, the newly formed cells may

be more embryonal than the older cells and the lesion may grow as a basal cell epithelioma

A close relation exists not only between tricho epithelioma and basal cell epithelioma, but also between tricho epithelioma and other types of benign epitheliomas such as syringoma and cylindroma Tricho epithelioma may occur with syringoma or cylindroma in the same patient (see pages 356, 358)

CALCIFYING EPITHELIOMA (MALHERBE)

Calcifying epithelioma is a solitary hard, deep seated tumor which is covered by normal skin It occurs most frequently on the face and



Fig 190 Calcifying epithelioma (Malherbe) The tumor consists of lobules embedded in a connective tissue stroma Two types of cells compose the lobules basophilic cells and shadow cells The basophilic cells resemble the cells of basal cell epithelioma The shadow cells show a central unstained shadow at the site of the nucleus In the center of the field one can see transformation of the basophilic cells into shadow cells The stroma contains numerous foreign body giant cells (×100)

the upper extremities The size is from 0 5 to 3 or even 5 cm in diameter

Histopathology Calcifying epithelioma is a sharply demarcated, often encapsulated tumor and usually located in the lower dermis

or in the subcutaneous fat The histologic appearance is characteristic Embedded in a connective tissue stroma variously shaped masses of epithelial cells are present As a rule two types of cells—basophilic cells and shadow cells —compose these masses (Fig 190) Occasionally basophilic cells are absent The basophilic cells greatly resemble the cells of basal cell epithelioma They possess



Fig 191 Calcifying epithelioma (Malherbe) Small and large areas of calcification are present within the lobules of shadow cells (×100)

large round or elongated deeply basophilic nuclei and only little cytoplasm so that the nuclei are densely packed The cellular borders are often indistinct so that it appears as if the nuclei were embedded in a symplasmic mass The shadow cells stain pale pink with hematoxylin-eosin They have a distinct border but take no nuclear staining Instead they show a central unstained shadow at the site of the nucleus In some areas one can see clearly that the shadow cells develop from the basophilic cells (Fig 190) In tumors of recent origin numerous areas of basophilic cells are usually present As the lesion ages the number of basophilic cells decreases due to their development into shadow cells and in tumors of long standing few or no basophilic cells remain In addition to basophilic and shadow

cells, areas of cornification are present The cornification may occur as sheets of horn cells or as small, round *centers of cornification* Sheets of horn cells are found only within the masses of shadow cells while the small, round centers of cornification may lie within areas of basophilic cells as well as within the masses of shadow cells In occasional instances, melanin is present within the tumor The melanin may be located in either the basophilic cells, the shadow cells or the stroma (Turhan and Kramer, Lever and Griesemer)

The *stroma of the tumor usually shows a considerable foreign body giant cell reaction* adjacent to the masses of shadow cells A frequent but not constant feature is calcification (Fig 191) The calcium may be present in large sheets replacing the shadow cells or may be pres ent *as fine granules within the cytoplasm of shadow cells* Occasion ally, ossification of calcified areas takes place (Nicholson, Highman and Ogden) Malignant degeneration does not occur

Histogenesis. The histogenesis of calcifying epithelioma is not established fully Originally described by Malherbe and Chenantais as a calcified epithelioma of sebaceous glands, it has been variously regarded as a tumor of misplaced rests of sebaceous gland epithelium (Sutton and Sutton), as a basal cell epithelioma with degeneration instead of differentiation of cells (Fink, Muehlon) or as a growth intermediary between epidermal cyst and basal-cell epithelioma (Côte) Turhan and Kramer expressed the opinion that calcifying epithelioma arises from hair matrix cells They believe that the baso philic cells are hair matrix cells and that the formation of shadow cells represents *a form of keratinization, an attempt at hair shaft for* mation In support of their theory, these authors point out that the basophilic cells resemble hair matrix cells, that the small, round cen ters of keratinization observed in the epithelial formations of these tumors resemble cross sections of hair shafts and that the melanin in some of these tumors is analogous to the melanin found in normal hair Highman and Ogden have arrived at similar conclusions

Lever and Griesemer regard the basophilic cells in calcifying epi thelioma as primary epithelial germ cells with a tendency to differen tiation into keratotic hair cells The basophilic cells, thus, are as sumed to have a function akin to that of hair matrix cells, but, being less mature than hair matrix *cells, they produce not hair but* irregu lar masses of immature hair cells (shadow cells) Accordingly, in a classification of primary epithelial germ tumors, calcifying epitheli oma of Malherbe can be placed under those with differentiation toward hair structures (see Table 6, page 319)

Differential Diagnosis. Epidermal and sebaceous cysts may re semble calcifying epithelioma of Malherbe if their contents has un

dergone partial calcification and if they have ruptured and due to the resulting foreign body giant-cell reaction, have undergone partial disintegration They then share with calcifying epithelioma the presence of irregular islands of epithelial cells of areas of calcification and of a foreign body giant cell reaction However, basophilic cells and shadow cells are not found It should be remembered that old lesions of calcifying epithelioma may show no more basophilic cells so that then the presence of shadow cells alone is the decisive factor in favor of calcifying epithelioma

Differentiation of calcifying epithelioma from sebaceous cyst with secondary basal cell epithelioma also rests largely on the presence of shadow cells since the areas of basophilic cells in calcifying epithelioma resemble basal-cell epithelioma, however, in calcifying epithelioma the epithelial structures never show palisading of the peripheral-cell layer and often there are areas in which one can observe the transformation of basophilic into shadow cells

BASAL-CELL EPITHELIOMA

Basal-cell epithelioma may occur anywhere on the skin except on the palms and the soles However, the face—particularly the periorbital region—is by far the most common site of location The mucous membranes are never affected Although basal-cell epithelioma occurs usually as a single lesion multiple lesions are not infrequent In occa ...

present n ...

types of ... occur (1) nodulo-ulcerative basal cell epithelioma including rodent ulcer, (2) pigmented basal-cell epithelioma (3) morphea like or fibrosing basal-cell epithelioma and (4) ...

... rs first as ... telangi ... in size and underg...

... ulceration ...

ing ulcer ...

rodent ulcer ...

Pigmented basal-cell epithelioma differs from the nodulo ulcerative type only by the dark pigmentation of the lesion

Morphea like or fibrosing basal-cell epithelioma manifests itself as an only slightly elevated firm yellowish plaque with ill-defined borders over which the skin remains intact for a long time before finally ulceration occurs

threadlike, pearly border The patches usually show small areas of superficial ulceration and crusting, in addition, their center may show smooth, atrophic scarring

Basal cell epitheliomas cannot be produced experimentally like squamous cell carcinomas However, they can develop following prolonged administration of inorganic arsenic (Anderson) (see page 155) and, in rare instances, in areas of radiodermatitis (Anderson and Anderson) (see page 122) Furthermore, basal cell epitheliomas of the face occur much more frequently in areas with much sunshine, as in Australia and in the south of the United States, than in less sunny regions, such as England and the north of the United States

Basal cell epitheliomas do not metastasize, as a rule It seems, however, that exceptions to this rule occur (Montgomery, 1928, Foot Amersbach, Lattes and Kessler) Lattes and Kessler found a total of 20 cases of metastasizing basal cell epitheliomas reported in the literature Yet many authors doubt the occurrence of metastases in basal cell epithelioma Walther expressed the belief that cases reported as metastasizing basal cell epithelioma represent wrong diagnoses

Histogenesis. Several theories exist regarding the origin of basal cell epithelioma Krompecher, the original describer of basal-cell epithelioma stated in 1903 that he regarded these tumors as carcinomas of the *basal cells of the epidermis He believed that those* tumors which showed a tendency to gland formation imitated the embryonal gland formation of the basal cells Krompecher s view is still adhered to by many (Montgomery *1940, Teloh and Wheelock*) However, Krainz believed that only those basal cells which develop into glandular cells give rise to basal cell carcinoma Geschickter and Koehler shared this view They suggested the designation appendage cell carcinoma Mallory and Haythorn held the opinion that basal cell epitheliomas were carcinomas of hair matrix cells

Foot expressed the view that basal cell epitheliomas were carcinomas which develop from distorted primordia of dermal adnexa rather than from ordinary epidermal basal cells He stated that the tumors took origin from any or all three types of adnexal primordia i e, hair, sebaceous gland and sweat gland and imitated their embryonal development

The first author to express doubts that basal cell epitheliomas were carcinomas was Adamson who in 1911 stated that, in his opinion basal cell epitheliomas were nevoid tumors originating "from latent embryonic foci aroused from their dormant state at a later period of life" He believed that the latent embryonic foci usually were embryonic pilosebaceous follicles but occasionally were embryonic sweat ducts Several authors have since reached si

cently Wallace and Halpert have suggested that basal-cell epitheliomas are benign tumors either of the hair matrix or of the hair anlage and have proposed the term trichoma for them

It is the author's belief that basal-cell epitheliomas are not carcinomas and are not derived from basal cells but instead are nevoid

entiated anaplastic cells In accordance with the potentiality inherent in the primary epithelial germ to differentiate into sebaceous glands apocrine glands and hair differentiation in basal cell epitheliomas can be either toward sebaceous gland apocrine gland or hair structures (See histogenesis and classification of epidermal tumors page 317 and Table 6 page 319)

Pinkus recently has suggested that basal cell epitheliomas arise not from an embryonal rest such as the primary epithelial germ but from pluripotential cells which have formed during adult life and can like the primary epithelial germ differentiate in the direction of sebaceous glands apocrine glands and hair The fact that basal cell epithelioma occasionally arises in areas of radiodermatitis and following the ingestion of arsenic is cited by Pinkus as evidence (although it could as well be assumed that these agents merely stimulate dormant primary epithelial germs to active growth)

Hueck has pointed out that in basal cell epitheliomas the connective tissue stroma always shows a close relationship to the tumor and proliferates with it just as it does in benign fibro epithelial tumors and in adenomas On the other hand in carcinomas the connective tissue usually is stretched then tears until it finally disintegrates He therefore regards basal-cell epithelioma not as a carcinoma but as a solid adenoma

Histopathology The characteristic cell of basal-cell epithelioma has a large oval or elongated deeply basophilic nucleus and little cytoplasm The cytoplasm is often defined poorly so that it may appear as if the nuclei were embedded in a symplasmic mass The nuclei resemble those of the basal cells of the epidermis very closely but the cells of [illegible] lls by not hav [illegible]

I [illegible] true car cinc [illegible] is an invasive tumor in most instances Scattered islands of tumor cells are often found away from the main tumor deep in the dermis and even in [illegible]

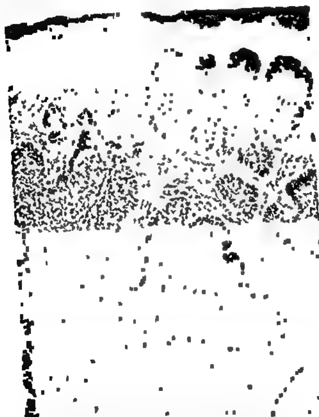
latter showing differentiation toward primary epithelial germ structures—i e toward sebaceous glands, apocrine glands or hair A sharp dividing line between the two groups cannot be drawn because many undifferentiated basal cell epitheliomas show differentiation in some areas and most differentiated basal cell epitheliomas show areas lacking differentiation Correlating the clinical with the histologic classification it can be stated that the *nodulo ulcerative type of basal-cell* epithelioma may be differentiated or undifferentiated whereas pigmented basal-cell epithelioma, fibrosing basal cell epithelioma and superficial basal cell epithelioma usually are undifferentiated. If the nodulo ulcerative basal cell epithelioma shows no differentiation it is called solid basal cell epithelioma if it shows differentiation it may be either a cystic an adenoid or a keratotic basal cell epithelioma

1 UNDIFFERENTIATED BASAL CELL EPITHELIOMAS The group of undifferentiated basal cell epitheliomas includes the solid basal cell epithelioma the pigmented basal cell epithelioma the morphea like or fibrosing basal cell epithelioma and the superficial basal cell epithelioma

A SOLID BASAL CELL EPITHELIOMA (primordial type of basal cell epithelioma Foot) *In this form variously sized and shaped masses* of tumor cells are embedded in the dermis (Fig 192) Some of the masses originate from the surface epider[illegible] no connections with it even on serial sections [illegible] sees a mass of tumor cells originate from [illegible] licle In the masses of tumor cells the n[illegible] of cells often show palisade arrangement whereas the nuclei of the cells inside lie in haphazard fashion

A mild or moderately severe inflammatory reaction may be present in the dermis particularly in the more rapidly growing tumors but it may be entirely lacking The connective tissue frequently proliferates with the tumor and is arranged in parallel bundles around the tumor masses so that a definite mutual relationship seems to exist between the parenchyma of the tumor and its stroma (*Hueck Pinkus*) *The connective tissue nearest to the tumor masses often* undergoes mucinous degeneration Since mucin shrinks during fixation the stroma frequently retracts from the tumor islands so that in prepared sections the tumor islands seem to lie free in cavities (Fig 201) Although this retraction represents merely an artefact caused by shrinkage during fixation it is quite *typical of basal cell* epithelioma and aids in [illegible] tumors such as squamous cell *carcinoma* [illegible] l cell epithelioma often is atrophic. [illegible] ulcer)

Some basal-cell epitheliomas with little or no structural differentiation toward the cutaneous appendages show evidence nevertheless of cellular differentiation by presenting two types of cells One type of cell has small, elongated, deeply basophilic nuclei, the other has



[illegible] solid basal-cell epithelioma (undifferentiated or primordial basal-cell [illegible]

large [illegible]

[illegible] secretory cells of either sebaceous or apocrine glands

B PIGMENTED BASAL-CELL EPITHELIOMA Although the presence of melanin can be demonstrated by silver stains in many basal-cell epitheliomas (Becker) large amounts are encountered only rarely The

presence of melanin in basal cell epitheliomas can be explained by the fact that melanin producing melanocytes are present not only in the surface epidermis but also in the primary epithelial germ (As the primary epithelial germ matures into the hair these melanocytes arrange themselves among the hair matrix cells overlying the hair papilla and form the melanin of the hair (See Fig 9)

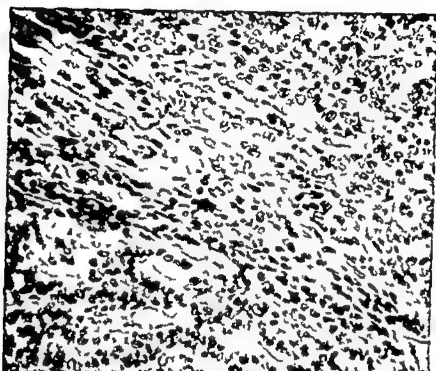


FIG. 193 Basal cell epithelioma with differentiation into two types of cells One type of cell has large oval pale nuclei the other type has small elongated dark nuclei (×400)

Basal cell epitheliomas with large amounts of pigment contain interspersed between the tumor cells numerous melanin laden melanocytes (Bloch) The connective tissue of these tumors contains numerous melanophores (Eller and Anderson Becker Toot)

C MORPHEA LIKE OR FIBROSING BASAL CELL EPITHELIOMA In this variant connective tissue proliferation is much greater than in the other types of basal cell epithelioma Embedded in a dense fibrous stroma one observes innumerable groups of closely packed tumor cells arranged in elongated strands (Fig 194) (Caro and Howell) Most of the strands are small but others are larger and show branching The groups of tumor cells often extend deeply into the dermis

D SUPERFICIAL BASAL CELL EPITHELIOMA This type of basal cell epithelioma originates from the epidermis in multiple foci (Fig 195)

The peripheral-cell layer of the budlike proliferations usually shows palisade arrangement There is little penetration into the dermis It may be pointed out that the epidermal buds often show great resemblance to the primary epithelial germ buds as seen in the em



FIG 191 Morphea like or fibrosing basal cell epithelioma Innumerable small groups of closely packed tumor cells many of them arranged in elongated strands are embedded in a dense fibrous stroma (×100)

bryonal skin (see Figure 1) The overlying epidermis usually shows atrophy but may show acanthosis and papillomatosis A mild to moderate amount of inflammatory infiltrate composed of lymphocytes and plasma cells is present in the upper dermis (Wise Montgomery 1929)

Some superficial basal-cell epitheliomas after having persisted as such for various lengths of time become true invasive basal-cell epi

presence of melanin in basal cell epitheliomas can be explained by the fact that melanin producing melanocytes are present not only in the surface epidermis but also in the primary epithelial germ (As the primary epithelial germ matures into the hair these melanocytes arrange themselves among the hair matrix cells overlying the hair papilla and form the melanin of the hair (See Fig 9)

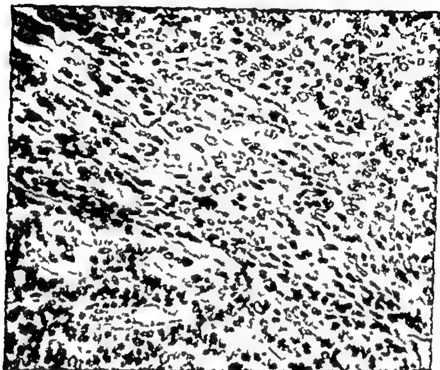


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Fig. 133. Morphea-like or fibrosing basal-cell epithelioma. Innumerable small *groups of closely* packed tumor cells, many of them arranged *in elongated* strands, are embedded in a dense fibrous stroma. (×100)

bryonal skin (see Figure 1). The overlying epidermis usually shows atrophy but may show acanthosis and papillomatosis. A mild to moderate amount of inflammatory infiltrate composed of lymphocytes and plasma cells is present in the upper dermis (Wise, Montgomery, 1929).

Some superficial basal-cell epitheliomas, after having persisted as such for various lengths *of time*, become truly invasive basal-cell epi

theliomas Since this change may at first be limited to a few areas, representative sections throughout the entire tissue block should be examined

A rare type of superficial basal cell epithelioma is the intra epidermal type In this type, the epidermis shows acanthosis Embedded in the broadened epidermis one finds multiple, sharply demarcated foci of basal cell epithelioma The tumor cells stand out clearly from the surrounding epidermis by their strongly basophilic staining (Montgomery, 1929, Sims and Parker)

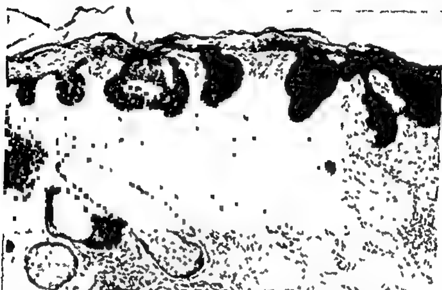


Fig 195 Superficial basal cell epithelioma The tumor shows multiple points of origin from the epidermis Note the similarity between the tumor buds in this illustration and the primary epithelial germ buds in the embryonal skin shown in Figure 1 (×100)

2 Differentiated Basal Cell Epitheliomas Differentiation in basal cell epitheliomas may proceed in three directions toward *sebaceous glands apocrine glands or hair* (Foot, Lever) Those with differentiation toward sebaceous glands are called cystic those with differentiation toward apocrine glands are called adenoid, and those with differentiation toward hair are called keratotic basal-cell epitheliomas In most differentiated basal cell epitheliomas, differentiation is directed toward more than one of the three structures For example, areas of keratinization may be found *in* a tumor which also shows glandular structures

A Cystic Basal Cell Epithelioma In this type, cystic spaces are present in the center of the tumor masses The cysts may form in three ways by degeneration of stroma that has become enclosed into the tumor, by degeneration of the center of the tumor masses, and

by differentiation of the cells in the center of the tumor masses to

the vicinity of the cyst are apt to be vacuolated (Foot) or even foamy (Pierard and Dupont) (Fig 196)

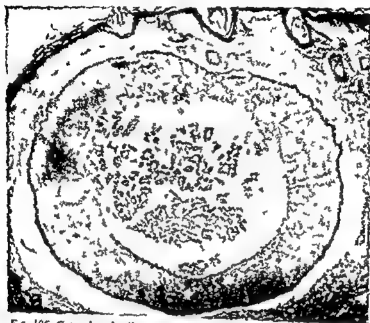


Fig 196 Cystic basal-cell epithelioma The cyst has formed by disintegration of cells with sebaceous differentiation (×50)

B ADENOID BASAL-CELL EPITHELIOMA This type of tumor shows formations suggesting *tubular* glandlike structures The cells are arranged in intertwining strands and radially around islands of connective tissue resulting in a *lacelike* patterning of the tumor (Fig 197) In some tumors one may find *lumina* surrounded by cells which have been ...

C KERATOTIC BASAL-CELL EPITHELIOMA (pilar type Foot) In this type cells with elongated nuclei and slightly eosinophilic cytoplasm are seen traversing the tumor as short bands or are arranged in concentric layers around *parakeratotic* or keratotic centers As pointed out by Krompecher who first described this type of basal-cell epi

Fig 197 Adenoid basal-cell epithelioma The strands of epithelial cells show a "lacelike" pattern The stroma shows mucoid degeneration (×200)

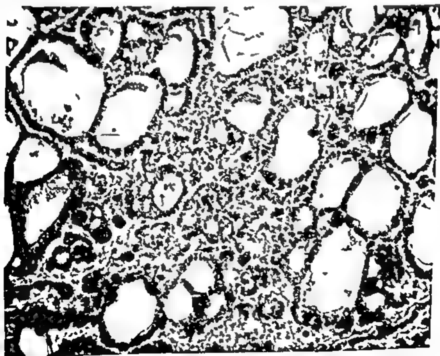


Fig 198 Adenoid basal-cell epithelioma The tumor contains lumina surrounded by cells that have the appearance of glandular cells (×200)

thelioma the elongated cells cornify abruptly so that the parakeratotic or keratotic centers are sharply demarcated against the surrounding cells (Fig 199)

totic or parakeratotic centers in keratotic basal-cell epithelioma develop from hair matrix cells and represent attempts at hair shaft formation (Foot) The keratinization in keratotic basal cell epithelioma thus is one of hair matrix cells which are cells without prickles and not one of squamous cells

Some keratotic basal-cell epitheliomas possess large centers of keratinization so-called horn cysts (Fig 200) They are like those observed in tricho-epithelioma (page 363) These horn cysts must not be confused with the horn pearls that occur in squamous cell carcinoma (see below under differential diagnosis)

BASAL SQUAMOUS CELL EPITHELIOMA Several authors (Darier and Ferrand Montgomery 1928 Juon) have described basal-cell epitheliomas with features of squamous-cell carcinoma According to Montgomery they represent metamorphosis of basal-cell to squamous-cell epitheliomas He stated that from 15 to 20 per cent of all basal-cell epitheliomas present such changes

Two types of basal squamous cell epithelioma are recognized by the authors named above a mixed and an intermediary type The mixed type is described as showing partial horn pearl formation with a parakeratotic rather than a horny center The intermediary type is described as showing two kinds of cells those with small elongated deeply basophilic nuclei regarded as basal cells and those with large round pale staining nuclei regarded as intermediary in character between basal and squamous cells

The existence of basal squamous-cell epithelioma is not generally accepted (Lever Welton Elliott and Kimmelstiel Lennox and Wells) It is likely that the mixed type of basal squamous-cell epithelioma represents a keratotic basal-cell epithelioma (Fig 199) and the intermediary type a solid basal-cell epithelioma in which the cells with large round pale staining nuclei show differentiation toward secretory cells of either sebaceous or apocrine glands (Fig 193) see page 373)

MIXED CARCINOMA These tumors

Like other chronic ulcerative



Fig 197 Adenoid basal cell epithelioma The strands of epithelial cells show a "lacelike" pattern The stroma shows mucoid degeneration (×200)

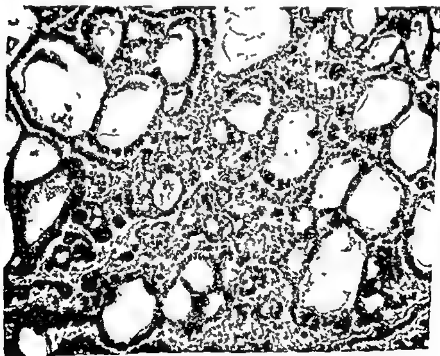


Fig 198 Adenoid basal cell epithelioma The tumor contains lumina surrounded by cells that have the appearance of glandular cells (×200)

However, they ng much more it to remember that keratinization is not a prerogative of squamous cell carcinoma



tains unusually large horn cysts. (×50)

but occurs also in basal-cell *epitheliomas* with differentiation toward hair structures (See "*Keratotic Basal Cell Epithelioma*," page 377.) Keratinization in basal-cell *epitheliomas* may be partial ("parakeratotic centers") or complete ("horn cysts"). The keratinization differs from that seen in the horn pearls of squamous-cell carcinomas by occurring abruptly without the *interposition* of gradually keratinizing squamous cells. The fairly common presence in basal-cell epithelioma of areas of retraction of *the tumor* cell masses from the sur-

lesions (for instance, lupus vulgaris, gumma and burns), basal cell epithelioma may stimulate the development of a squamous cell carcinoma. Before making a diagnosis of "mixed carcinoma," one must rule out the possibility of pseudo epitheliomatous hyperplasia occurring in a basal-cell epithelioma (see page 334).

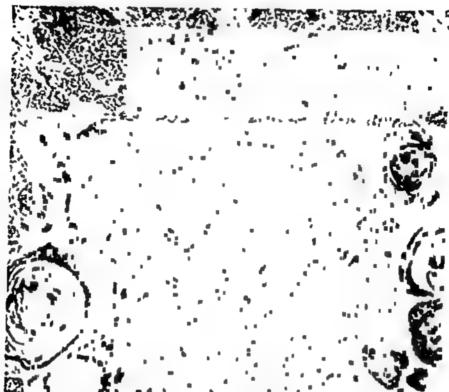


FIG 199 Keratotic basal cell epithelioma (pilar type of basal cell epithelioma) The cell masses in this tumor are composed largely of elongated cells lying in concentric arrangement Several of the cell masses contain a horn cyst in their center The elongated cells contain no prickles they represent hair matrix cells Note the abrupt and *complete keratinization in the horn cysts* (×100)

Differential Diagnosis. Differentiation of basal cell epithelioma from squamous cell carcinoma may be difficult at times—so difficult that many authors have decided that intermediary forms ("basal squamous cell epithelioma") occur As a rule, however, differentiation is fairly easy. One of the best points of differentiation is that the cells of basal cell epithelioma stain deeply basophilic, whereas most cells of squamous cell carcinoma at least in Grades I and II, have an eosinophilic tint due to partial or complete keratinization In squamous cell carcinoma, Grades III and IV, the cells, because of

noid type (Hooley) The former type is more common than the lat

the same lesion

ia shows considerable

The acanthosis is due

entirely to upward growth of epithelial cells Thus, the lower base of the tumor lies above a straight line that may be drawn from the normal epidermis at one end of the tumor to the normal epidermis at the other end and the lesion appears as though tacked on the sur



Fig 202 Basal-cell papilloma, keratotic type. Low magnification The superficial location of the tumor is apparent The lesion appears as if tacked on the epidermis (X25)

tracts of epithelial cells surrounding islands of connective tissue The horny layer invaginates in places deep into the lesion Because of the tortuosity of these invaginations, cystic inclusions of horny material result (Fig 203) They are surrounded by a shell of squamous cells

a small amounts

It is located in

clear cells") are

prominent in the pigmented portions

The adenoid type of basal-cell papilloma shows, originating from the epidermis numerous thin tracts composed of a double row of cells These cells resemble those of basal-cell epitheliomas The tracts

rounding connective tissue (see page 372) also aids in differentiating it from squamous cell carcinoma, since such areas of retraction are not found in the latter.

The differential diagnosis between basal cell epithelioma and tricho epithelioma already has been discussed (see page 364)

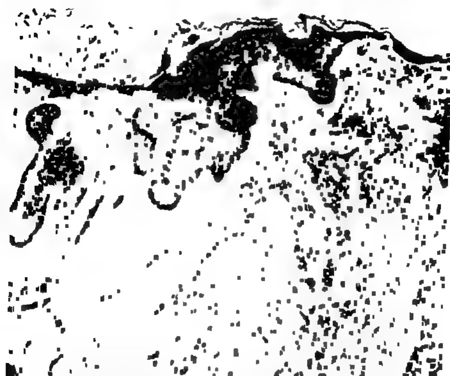


FIG 201 "Mixed carcinoma" A basal cell epithelioma (*left*) and a squamous cell carcinoma (*right*) lie side by side (×50)

BASAL CELL PAPILLOMA (VERRUCA SENILIS, KERATOSIS SEBORRHEICA)

Basal cell papillomas develop, often in large numbers, on the trunk, the face and the arms in persons past middle life They are sharply circumscribed, slightly raised, verrucous, more or less pigmented lesions which often look as if "stuck on" the surface of the skin The verrucous covering of the lesions tends to have a soft, greasy consistency Although most lesions measure only a few millimeters in diameter, an occasional lesion may reach a size of several centimeters.

Histopathology. *This tumor represents a squamous cell papilloma in which there are areas of proliferation of cells of the same type as seen in basal-cell papilloma*

Basal cell papillomas occur in two types a keratotic and an ade

noid type (Hookey) The former type is more common than the lat
he same lesion
ia shows considerable
The acanthosis is due
entirely to upward growth of epithelial cells Thus the lower base of the tumor lies above a straight line that may be drawn from the normal epidermis at one end of the tumor to the normal epidermis at the other end and the lesion appears as though tacked on the sur



FIG. 202. Basal-cell papilloma keratotic type Low magnification The superficial location of the tumor is apparent. The lesion appears as if tacked on the epidermis. (X25)

face of the skin (Fig 202) The acanthosis is due in part to prolifera tion of sq am

interwoven
tracts of epithelial cells surrounding islands of connective tissue The horny layer invaginates in places deep into the lesion Because of the tortuosity of these invaginations cystic inclusions of horny material result (Fig 203) They are surrounded by a shell of squamous cells Melan
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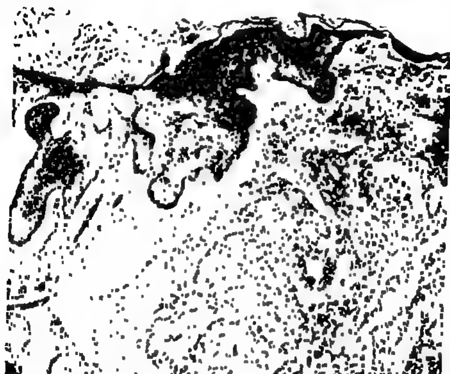


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Histopathology. This tumor represents a squamous cell papilloma in which there are areas of proliferation of cells of the same type as seen in basal-cell papilloma

Basal-cell papillomas occur in two types. a keratotic and an ade-

branch and interweave (Fig 204) Considerable amounts of melanin usually are present in the tracts Cystic inclusions of horny material are absent The demarcation at the lower border is sharp just as in the keratotic type of basal-cell papilloma

Although basal-cell papilloma shows no tendency to invasion of the dermis it may be regarded as related to basal-cell epithelioma because a large proportion of the cells are of the same type as found in basal-cell epithelioma However actual change of basal cell papilloma into a frank basal cell epithelioma with deep invasion and ulceration is rare (Fller and Ryan Pinkus)

(For differential diagnosis from nevus verrucosus see page 322 and from keratosis senilis see page 328)

Dermatosis Papulosa Nigra

This condition is frequent among Negroes especially females The lesions are located on the face especially in the malar regions and consist of minute soft rounded usually hyperpigmented papules

Histopathology The histologic changes are the same as in basal cell papilloma Melanin pigmentation of the basal layer is pronounced (Michael and Seale)

CARCINOMA OF SEBACEOUS GLANDS

Carcinomas of sebaceous glands have been described occasionally in the literature Some authors are more inclined to make this diagnosis than others Warren and Warvi for instance reported 28 personally observed cases while most other authors have reported only single instances (Beach and Severance)

Carcinomas of sebaceous glands occur most frequently on the eyelids originating from meibomian glands which are modified [illegible]

[illegible] anywhere.

[illegible] picture

[illegible] ion consists

[illegible] one observes definite lobular formations (Fig 205) Although many cells are undifferentiated distinct sebaceous cells are present Mitotic figures are numerous Lipid material can be demonstrated not only in the sebaceous cells but also as fine globules in many other cells of the tumor Beach and Severance state that the undifferentiated cells of sebaceous carcinoma differ from those of basal-cell [illegible]

Fig 203 Basal cell papilloma Keratotic type High magnification Thick interwoven tracts of basal cells compose the tumor Interspersed are cystic inclusions of horny material caused by invaginations of the horny layer (×100)

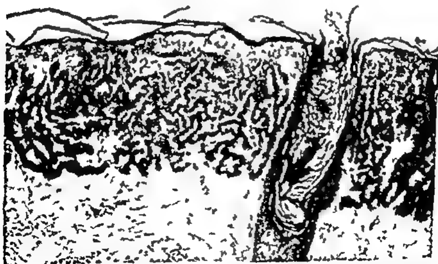


Fig 204 Basal cell papilloma adenoid type Thin interwoven tracts composed of a double row of basal cells compose the tumor No cystic inclusions of horny material are present (×100)

branch and interweave (Fig 204) Considerable amounts of melanin usually are present in the tracts Cystic inclusions of horny material are absent The demarcation at the lower border is sharp just as in the keratotic type of basal cell papilloma

Although basal-cell papilloma shows no tendency to invasion of the dermis it may be regarded as related to basal cell epithelioma because a large proportion of the cells are of the same type as found in basal cell epithelioma However actual change of basal cell papilloma into a frank basal-cell epithelioma with deep invasion and ulceration is rare (Fller and Ryan Pinkus)

(For differential diagnosis from nevus verrucosus see page 322 and from keratosis senilis see page 328)

Dermatosis Papulosa Nigra

This condition is frequent among Negroes especially females The lesions are located on the face especially in the malar regions and consist of minute soft rounded usually hyperpigmented papules

Histopathology The histologic changes are the same as in basal cell papilloma Melanin pigmentation of the basal layer is pronounced (Michael and Seale)

CARCINOMA OF SEBACEOUS GLANDS

Carcinomas of sebaceous glands have been described occasionally in the literature Some authors are more inclined to make this diagnosis than others Warren and Warvi for instance reported 28 personally observed cases while most other authors have reported only single instances (Beach and Severance)

Carcinomas of sebaceous glands occur most frequently on the eyelids, originating from meibomian glands which are modified sebaceous glands (Hagedoorn) they may however occur anywhere on the skin (Beach and Severance) No character [illegible]

[illegible] observes definite lobular formations (Fig 205) Although many cells are undifferentiated distinct sebaceous cells are present Mitotic figures are numerous Lipid material can be demonstrated not only in the sebaceous cells but also as fine globules in many other cells of the tumor Beach and Severance state that the undifferentiated cells of sebaceous carcinoma differ from those of basal cell epithelioma by showing greater variation in size and shape and by having a more acidophilic cytoplasm and a lighter staining nucleus

It seems that many cases reported as sebaceous carcinoma may be regarded as sebaceous adenoma (see page 347) or as sebaceous epithelioma, which is a basal cell epithelioma with considerable differentiation of the cells toward sebaceous gland cells (page 353). For in



FIG 205 Carcinoma of sebaceous glands Closely packed lobular formations are present in the dermis They are composed of sebaceous and undifferentiated cells Some of the latter are atypical (×200)

stance, the five cases of sebaceous carcinoma reported by Savatard as arising in cases of nevus sebaceus are best classified as instances of sebaceous epithelioma

CARCINOMA OF ECCRINE SWEAT GLANDS

Carcinomas of the eccrine sweat glands are rare, but their existence seems to be established definitely They do not possess a characteristic appearance, either clinically or histologically

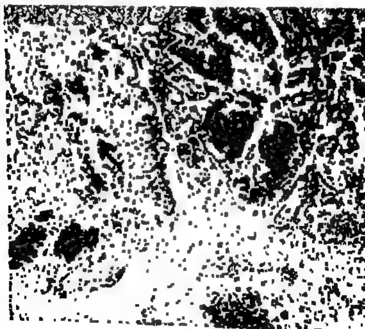
Histopathology. It is difficult to recognize carcinoma of eccrine sweat glands and to differentiate it from other cutaneous tumors, [illegible]

[illegible] carcinomas of sweat glands [illegible], cystic papillary and solid forms. He pointed out that combinations of these forms were frequent. He recognized the occasional occurrence of metaplasia of glandular cells into squamous and horn cells.

ADENOACANTHOMA OF SWEAT GLANDS

Carcinomas of sweat glands with glandular as well as epidermal elements have recently been reported under the designation adenoacanthoma of sweat glands (Lever).

Clinically, these tumors resemble squamous-cell carcinoma. They show shallow central ulceration and may have a verrucous surface. Their site of predilection is the face, especially the ears.



[illegible] noma of sweat glands [illegible]

[illegible] the alveolar formations an island of tumor tissue and several atypical sweat glands or ducts are present. (×50)

Histopathology. *Adeno* acanthomas show tubular and alveolar lumina lined with one or several layers of epithelium (Fig 206) In areas where the lumina are lined with a single layer of epithelium the epithelial cells have the appearance of glandular cells, but in areas with several layers of epithelium, squamous and partially keratinized cells usually form the inner layers The lumina are filled with



Fig 207 Adeno acanthoma of sweat glands High magnification of the atypical sweat glands or ducts seen in Figure 206 Papillary tufts protrude into their lumina These sweat glands approach in appearance the glandular structures belonging to the tumor (×200)

desquamated cells, many of which are partially or completely keratinized In addition there are solid areas which have the appearance of squamous cell carcinoma Atypical eccrine sweat glands and sweat ducts are present within or at the periphery of these tumors (Fig 207)

Histogenesis. The author originally regarded these tumors as sweat gland carcinomas composed of glandular and epidermal elements and explained the presence of these two structures by the fact that sweat ducts are composed of squamous cells in their epidermal portion, and of glandular cells in the dermis It is possible, however, that these tumors are squamous cell carcinomas of alveolar growth in which there is considerable individual cell keratinization resulting in acantholysis in the center of the alveolar formations

Borelli regards these tumors as dyskeratotic squamous-cell carcinomas which arise from the hair follicle and tend to imitate the structure of glands which develop embryologically together with the follicle

CARCINOMA OF APOCRINE GLANDS

Extramammary Paget's disease represents a carcinoma of apocrine glands (see page 339) No other form of carcinoma of apocrine glands has so far been established

METASTATIC CARCINOMA OF THE SKIN

Cutaneous metastasis of carcinoma is rare with the exception of carcinoma of the breast Next to carcinoma of the breast metastases

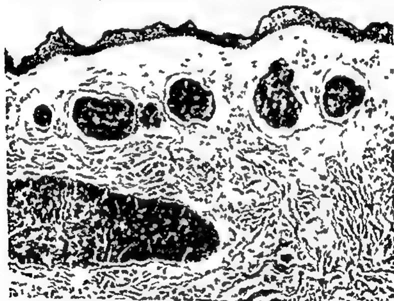


Fig 208 Metastatic carcinoma of the skin from carcinoma of the breast Inflammatory carcinoma The dermal lymphatics are filled with clusters of tumor cells (×100)

to the skin are observed most frequently in carcinoma of the stomach the uterus the lungs the large intestines and the kidneys in that order (Gates) In occasional instances cancer of [illegible]

[illegible] lead to cutaneous metastases

Dissemination may take place through the lymphatics or through the blood stream In carcinoma of the breast cutaneous metastases

Histopathology Adenoacanthomas show tubular and alveolar lumina lined with one or several layers of epithelium (Fig 206) In areas where the lumina are lined with a single layer of epithelium the epithelial cells have the appearance of glandular cells but in areas with several layers of epithelium squamous and partially keratinized cells usually form the inner layers The lumina are filled with

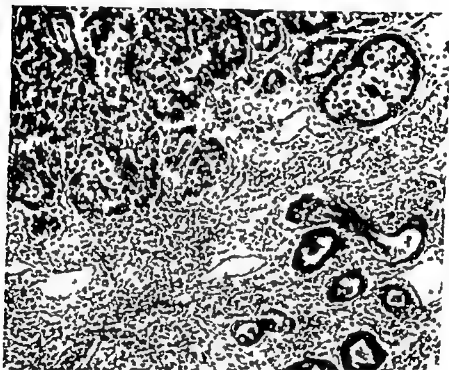


Fig 207 Adenoacanthoma of sweat glands High magnification of the atypical sweat glands or ducts seen in Figure 206 Papillary tufts protrude into their lumina These sweat glands approach in appearance the glandular structures belonging to the tumor (×200)

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Histogenesis The author originally regarded these tumors as sweat gland carcinomas composed of glandular and epidermal elements and explained the presence of these two structures by the fact that sweat ducts are composed of squamous cells in their epidermal *portion* and of glandular cells in the dermis It is possible however that these tumors are squamous-cell carcinomas of alveolar growth in which there is considerable *individual cell keratinization* resulting in acantholysis in the center of the alveolar formations

In inflammatory carcinoma the skin of the affected breast and the adjoining areas present erythema and diffuse edema simulating erysipelas. In telangiectatic carcinoma the skin contains numerous purplish papules and hemorrhagic pseudovesicles resembling hemolymphangioma. In cancer en cuirasse the skin of the breast affected by the carcinoma and often also the surrounding skin shows dif-



FIG 210 Metastatic carcinoma of the skin from carcinoma of the breast. Cancer en cuirasse, indurated area. Only few tumor cells are present. They lie embedded between collagen bundles in single row lines. Because of their small number and size they may be overlooked easily. (×400)

fuse brawny induration interspersed with nodules and punched out ulcerations.

Histopathology. In inflammatory carcinoma histologic examination of the skin reveals extensive invasion of the dermal lymphatics—especially of the subepidermal lymphatics—by groups and cords of tumor cells (Fig 208) (Taylor and Meltzer). The tumor cells are similar to those of the primary growth, atypical in character, with large rounded deeply staining nuclei and a moderate amount of cytoplasm. Occasional mitoses are seen in these cells. There is marked capillary congestion (which is the reason for the inflammatory appearance clinically). In addition, one observes edema and a slight perivascular lymphocytic infiltrate in the dermis but no fibrosis (Pfahler and Case).

usually are caused by way of the lymphatics In other carcinomas, cutaneous metastases, as a rule, are caused by dissemination through the blood stream, although occasionally dissemination takes place through lymphatics secondary to local lymph node involvement (Gates)



FIG 209 Metastatic carcinoma of the skin from carcinoma of the breast Cancer en cuirasse nodular lesion There is considerable fibrosis of the dermis with small scattered islands of tumor cells Some of the islands show a suggestive glandular arrangement of the tumor cells (×200)

CUTANEOUS METASTASIS FROM CARCINOMA OF THE BREAST

Three types of cutaneous metastases may occur in carcinoma of the breast inflammatory carcinoma telangiectatic carcinoma, and cancer en cuirasse Two or all three of these types may be present in the same patient If dissemination of metastases through the lymphatics proceeds rapidly inflammatory carcinoma results in most instances, and telangiectatic carcinoma in rare instances If dissemination proceeds slowly, cancer en cuirasse eventuates (Taylor and Meltzer)

Histopathology Large and small groups of tumor cells are present throughout the dermis As a rule no tumor cells are found within capillaries or lymphatics A certain amount of fibrosis is usually present Signs of inflammation are absent (Gates)

The metastatic carcinoma readily can be classified as either an adenocarcinoma (Fig 211) a squamous-cell carcinoma or an undifferentiated carcinoma However, it is only occasionally possible to draw conclusions from the histologic appearance of the metastasis as to the site of the primary tumor For instance if the tumor cells of the cutaneous metastasis contain mucin the primary carcinoma most likely resides in the gastro intestinal tract The mucin-containing cells present in the metastasis appear just as in the primary tumor as so-called signet ring cells--namely, as large round cells filled with mucin which presses the nucleus against the cellular wall (Fig 212

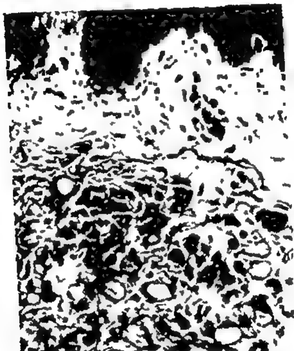


Fig 212 Metastatic carcinoma of the skin originating from the stomach Many of the tumor cells are so-called *signet ring cells* in which on account of the presence of mucin in the cytoplasm the nucleus is pressed against the cell wall (×400)

In telangiectatic carcinoma, the dilated lymphatics contain in addition to groups of tumor cells, varying amounts of erythrocytes (Freeman and Lynch, Leavell and Tillotson) The frequent location of these lymphatics immediately beneath the epidermis causes the clinical resemblance of the lesions to vesicles

In cancer en cuirasse, the nodular areas usually contain large and small groups as well as sheets of tumor cells lying outside of lymphatics in the dermis and surrounded by fibrosis (Fig 209) However, the indurated areas often contain only few tumor cells which therefore, may be easily overlooked The tumor cells are small angular and deeply basophilic and lie as single cells in single row lines or small groups between thickened collagen bundles The arrangement in single row lines, like Indians in a file, is of particular diagnostic importance (Fig 210)

Cutaneous Metastasis from Carcinomas Other than Breast Carcinoma

The cutaneous metastases caused by carcinomas of organs other than the breast occur clinically as circumscribed nodules or tumors The nodules are usually discrete and moderately firm Their number may vary *from one to several hundred*

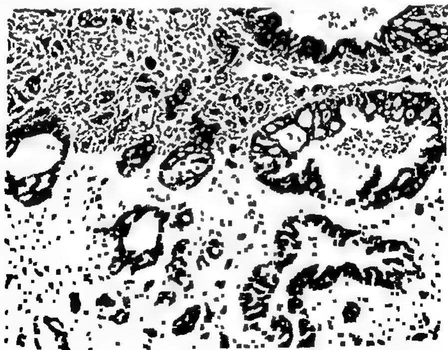


Fig. 211 Metastatic adenocarcinoma of the skin Numerous lumina are present (×100)

Histopathology. Large and small groups of tumor cells are present throughout the dermis As a rule, no tumor cells are found within capillaries or lymphatics A certain amount of fibrosis is usually present Signs of inflammation are absent (Gates)

The metastatic carcinoma readily can be classified as either an adenocarcinoma (Fig 211), a squamous-cell carcinoma or an undifferentiated

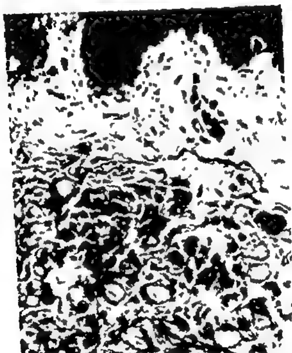


Fig 212 Metastatic carcinoma of the skin originating from the stomach Many of the tumor cells are so-called signet ring cells in which on account of the presence of mucin in the cytoplasm the nucleus is pressed against the cell wall (×400)

entiated carcinoma However, it is only occasionally possible to draw conclusions from the histologic appearance of the metastasis as to the site of the primary tumor For instance, if the tumor cells of the cutaneous metastasis contain mucin, the primary carcinoma most likely resides in the gastro intestinal tract The mucin-containing cells present in the metastasis appear, just as in the primar[illegible] as so-called [illegible]

mucin

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19

Mesodermal Tumors

The mesodermal tumors occurring in the skin may be divided into (1) tumors of fibrous tissue (2) tumors of mucoid tissue (3) tumors of fatty tissue (4) tumors of nerve tissue, (5) tumors of vascular tissue (6) tumors of muscular tissue and (7) tumors of osseous tissue Inclusion of tumors of nerve tissue under mesodermal tumors is of course not entirely correct but appears justified because mesodermal nerve sheath cells seem to represent an important component of most of the cutaneous tumors of nerve tissue

Benign and malignant tumors occur The malignant tumors of mesodermal tissue are called sarcomas They are almost invariably single tumors Involvement of other organs takes place by way of metastasis

Old classifications formerly recognized spindle cell sarcoma and round cell sarcoma The term spindle-cell *sarcoma* is *synonymous* with fibrosarcoma Round cell sarcomas are no longer classified as such but as lymphomas (i e stem-cell reticulum-cell lymphoblastic and lymphocytic lymphoma see page 471) Lymphomas differ from sarcomas by their potentially systemic nature which is demonstrated by the fact that frequently they arise in multiple foci Also the term melanosarcoma is no longer in use since the mother cell of the tumors formerly so designated is not a mesodermal cell The preferred term is malignant melanoma

I TUMORS OF FIBROUS TISSUE

DERMATOFIBROMA HISTIOCYTOMA (SCLEROSING HEMANGIOMA NODULAR SUBEPIDERMAL FIBROSIS)

This lesion occurs in the skin as firm indolent single or multiple nodules The nodules usually *arise in adults* and are situated most commonly on the extremities but occasionally elsewhere Although they are as a rule not larger than a few *millimeters* in diameter they may measure several *centimeters in size* Most lesions have a reddish color others are yellowish brown (because of the presence of large amounts of lipid) or bluish black (because of the *presence*

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the rete ridges In some instances, this proliferation results in budding formations resembling superficial basal-cell epithelioma. The subcutaneous fat is not invaded (Rentiers and Montgomery) Evidence of phagocytic activity is lacking and staining for iron and lipid gives negative results



FIG 213 Dermatofibroma Low magnification The collagen shows disorderly arrangement Much of the collagen is young and instead of staining bright red with hematoxylin eosin stains pale blue and instead of being assembled in firm bundles, lies in individual fibers A moderate number of fibroblasts and of capillaries are present (X50)

HISTIOCYTOMA In this lesion, in addition to fibroblasts, there are varying numbers of histiocytes They tend to lie in nests Occasionally the great majority of cells are histiocytes The histiocytes are larger cells than the fibroblasts and possess ample amounts of pale cytoplasm and ovoid rather than spindle ... Numerous newly form... may be present The ... amounts of lipid or

of large amounts of hemosiderin) In the latter case, the clinical appearance resembles that of a malignant melanoma

Histopathology. Histologically, the nodules can be divided into two types those composed entirely of fibroblasts (dermatofibroma) and those containing, in addition to fibroblasts, varying amounts of histiocytes (histiocytoma)

Various theories exist concerning the histogenesis of this lesion Originally described as dermatofibroma, Woringer, in 1932, proved the presence of phagocytic histiocytes in many dermatofibromas and proposed the term histiocytoma for those containing histiocytes He regarded histiocytomas as young dermatofibromas because of his belief that the histiocyte represents the parent cell of the fibroblast and may develop into a fibroblast (see page 33) Woringer's observations were supported by the studies of Senear and Caro who showed by vital staining with colloidal iron that some lesions which had histologically the appearance of dermatofibromas contained cells with phagocytic properties and thus were histiocytomas rather than dermatofibromas Gross and Wolbach, on the other hand, have emphasized the presence of blood vessels in these lesions and have expressed their belief that they represent sclerosing hemangiomas They regard the cells present in these lesions as proliferating endothelial cells which attempt to form new blood vessels but do not always succeed and instead become engulfed by regressive fibrosis It would seem however that the development of collagen in these tumors does not represent a regressive process but rather a progressive differentiation A still different view has been taken by Michelson and by Renters and Montgomery These authors believe that histiocytomas are not tumors at all but represent a chronic inflammatory proliferation of fibroblasts that may follow trauma They refer therefore to dermatofibroma and histiocytoma as nodular subepidermal fibrosis The presence of histiocytes is explained by them as a response to hemorrhage and local tissue destruction

DERMATOFIBROMA The nodule contains varying numbers of cells all of which are fibroblasts with spindle shaped nuclei Much of the collagen produced by these fibroblasts is young and instead of staining bright red with hematoxylin eosin it stains a pale blue and instead of being assembled in firm bundles it lies in individual fibers (see Plate 3) The fibroblasts and the collagen are arranged in paral

bands (Fig 213) The lesion is encapsulated, and nearly always

is separated from the overlying epidermis by a narrow band of normal collagen The epidermis may be normal or atrophic but commonly shows acanthosis with irregular downward proliferation of

the rete ridges In some instances this proliferation results in budding formations resembling superficial basal cell epithelioma The subcutaneous fat is not invaded (Rentiers and Montgomery) Evidence of phagocytic activity is lacking and staining for iron and lipid gives negative results



lagen shows disorderly arrangement Much of the collagen is young and instead of staining bright red with hematoxylin eo … bled in … number …

HISTIOCYTOMA In … varying numbers c… ally the great ma… are histiocytes The histiocytes are larger cells than the fibroblasts and possess ample amounts of pale cytoplasm and ovoid rather than spindle shaped nuclei (Fig 214) Numerous newly formed capillaries with prominent endothelial cells may be present The histiocytes contain varying amounts of lipid or

hemosiderin or both These substances can often be recognized without special staining but are much better visualized when special stains for iron and lipid are employed The lipid usually is doubly refractile Some tumors contain a fairly large number of true foam cells and even Touton giant cells Occasionally, one may find large foreign body giant cells which have developed from either histio

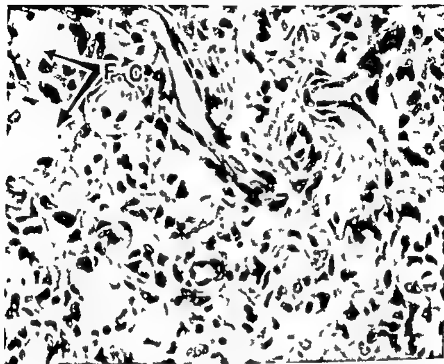


Fig 214 Histiocytoma The lesion is composed mainly of histiocytes There are numerous large and small blood vessels lined by prominent endothelial cells Several foam cells are present two particularly large foam cells (F C) can be seen in the upper left corner (×400)

cytes or endothelial cells (see below under Nevoxantho endothelioma, page 407)

Differential Diagnosis In rare instances, dermatofibromas show a considerable number of nuclei In such cases differentiation from fibrosarcoma especially dermatofibrosarcoma protuberans (see page 410) may cause difficulties However the circumscribed nature of the lesion especially the absence of invasion into the subcutaneous fat the lack of atypicality in the appearance of the nuclei and the absence of mitotic figures rule out sarcoma (Michelson)

Histiocytoma with many fat cells closely resembles xanthoma tuberosum in a regressive fibrosing stage and may even be indistinguishable from it (Arnold and Tilden) In such cases clinical data, such as the number and the location of the lesions and the

presence or the absence of hypercholesteremia are necessary to arrive at the correct diagnosis

Nevo xantho-endothelioma

Nevo xantho endothelioma is characterized clinically by the presence of a group or groups of yellowish brown nodules arising in early

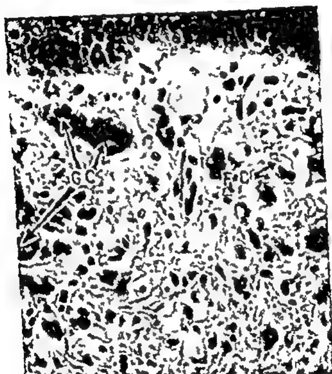


Fig. 215 Nevo-xantho-endothelioma The lesion is composed mainly of histiocytes Several foam cells (F C) and foreign body giant cells (G C) are present This lesion probably represents a form of histiocytoma (X400)

childhood usually on the extremities The lesions involute spontaneously within a few years

Histopathology Nevo xantho-endothelioma probably represents a young histiocytoma As in histiocytoma histiocytes predominate many histiocytes have a pale vacuolated cytoplasm and on staining for fat are shown to contain lipid Typical foam cells and Touton giant cells are present There are many capillaries showing proliferation of their endothelium In addition large foreign body giant cells

are present which originate either from histiocytes or from endothelial cells (Fig. 215)

Senear and Caro and Montgomery and Osterberg regard nevo xantho endothelioma as a variant of xanthoma However, since in patients with nevo xantho endothelioma the clinical and the blood chemical findings do not support a diagnosis of xanthomatosis, and since the histologic picture does not differ essentially from that of histiocytoma, it seems best to regard the lesion as a histiocytoma Nevo xantho endothelioma differs from histiocytoma only by showing foam cells and giant cells of the foreign body type in larger number.

Reticulo histiocytoma

This rare condition occurs as solitary or multiple, fairly large cutaneous nodules in adults The lesions may remain stationary or may involute.

Histopathology. The histologic picture is characterized by the presence of large, bizarre shaped, multinucleated giant cells with abundant, pale cytoplasm and vesicular nuclei They are separated from one another by fibrous connective tissue (Zak) Occasionally, it is possible to demonstrate the presence of fat within the cytoplasm of these cells Vital staining with colloidal iron indicates that the large cells have phagocytic properties and are reticulo endothelial in nature (Caro and Senear)

It is likely that reticulo histiocytoma is an unusual type of histiocytoma Caro and Senear assume that it is not a true neoplasm but actually a granuloma

KELOID

Keloids represent a post traumatic tissue proliferation They are red raised and firm and have a smooth, shiny surface Occasionally clawlike projections radiate from the edges of the lesions

Histopathology. Keloids cannot be differentiated from a dermato fibroma on a histologic basis In an early keloid one finds, in addition to thick, intertwining bundles of collagen a moderate number of fibroblasts (Fig 216) An old keloid may show but few cellular elements

FIBROSARCOMA

Fibrosarcoma occurs in the skin in two forms as true fibrosarcoma and as dermatofibrosarcoma protuberans However there is justifiable doubt that the latter represents a real sarcoma

True Fibrosarcoma

True fibrosarcoma starts only rarely in the dermis, more commonly, it starts in the subcutaneous fat (Broders, Hargrave and

Meyerding) The tumor usually feels firm and irregular on palpation and at first is covered by normal skin It usually grows quite rapidly and as it increases in size the overlying skin at first shows purplish discoloration and finally ulceration Satellite lesions frequently develop Metastases occur sooner or later They usually spread by way of the blood stream especially to the lungs The regional lymph nodes are involved only rarely (Gentele)

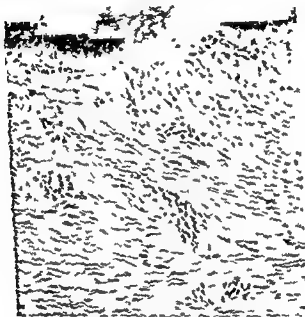


FIG 216 Keloid The lesion is composed of thick intertwining bundles of collagen The collagen is entirely mature and stains eosinophilic throughout A moderate number of nuclei are present therefore this keloid is of relatively recent genesis (X200)

Histopathology This tumor is very cellular The nuclei vary greatly in size shape and staining qualities Although most nuclei are spindle shaped others appear round or oval Some nuclei stain very dark while others appear vesicular with irregular chromatin structure Typical as well as atypical mitotic figures are present, often in large numbers The nuclei tend to lie in bundles that extend in various directions but do not form whorls In some areas the nuclei lie in dense clusters Thus fibrosarcomas present an extremely disorderly arrangement of the nuclei Usually these tumors contain some collagenous tissue in which the nuclei appear to be embedded

but highly malignant fibrosarcomas may possess little or no collagen. Instead, on staining with a reticulum stain, they are seen to contain numerous reticulum fibers (Foot).

Because of the invasive nature of these tumors, ulceration at the surface and infiltration into the subcutaneous tissue and underlying structures frequently are observed.

Differential Diagnosis. A highly malignant fibrosarcoma with no production of collagen may be difficult to differentiate from squamous cell carcinoma, Grade IV, amelanotic malignant melanoma, stem cell lymphoma or reticulum cell lymphoma. On thorough inspection, however, one will usually find, in squamous-cell carcinoma, Grade IV, some tendency to keratinization and connections of the tumor with the epidermis (page 331), in malignant melanoma, one will find "junction activity" at the epidermo-dermal border (page 458), while in stem cell and reticulum cell lymphoma spindle-shaped nuclear forms are absent, since all cells are "round cells" (see pages 474, 475).

Spindle-celled malignant tumors may form in areas of radiodermatitis. Although they have the morphologic appearance of a fibrosarcoma, it is likely that most, if not all, represent Grade IV spindle-celled squamous cell carcinoma (see page 333) (Gentele, Blom Ides).

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans represents a slowly growing tumor which has its origin in the dermis. It begins with one or several closely set small, hard nodules which are reddish or bluish. As the nodules coalesce, they form one or several plaques. On these plaques protruding tumors subsequently develop and may ulcerate.

Although this tumor is locally invasive as a rule, it does not give rise to metastases. In exceptional cases, metastases may occur many years after the appearance of the tumor. Binkley, for instance, reported a case in which metastases caused the death of the patient 38 years after the tumor had first appeared. Costa has expressed the belief that dermatofibrosarcoma protuberans was not truly malignant because of its slow rate of growth and the absence of metastases in most cases. He regards the tumor as intermediary between dermatofibroma and true fibrosarcoma, partaking of the nature of both. He prefers to call it progressive recurrent dermatofibroma.

Histopathology. The histologic appearance of the tumor does not differ materially from that of true fibrosarcoma (Binkley). A differentiation of the two tumors on a histologic basis, therefore, is not always possible. Just as in true fibrosarcoma, the nuclei lie in irregu

degeneration of the collagen is observed commonly in parts of the tumor (Binkley) Ulceration at the surface and invasion into the subcutaneous fat occur

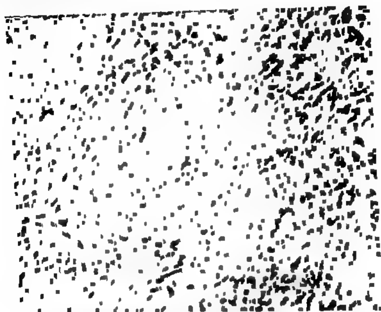


Fig 217 Dermatofibrosarcoma protuberans The nuclei of the fibroblasts are arranged in irregular strands and whorls They show a slight degree of atypicality In contrast with malignant fibrosarcoma formation of collagen is well in evidence (×200)

Differential Diagnosis For differentiation from dermatofibroma, see page 406

2 TUMORS OF MUCOID TISSUE

MYXOMA

Although fibromas and neurofibromas may undergo more or less complete mucoid degeneration and then present in such degenerated areas the aspect of myxoma myxomas may arise as such

Clinically myxomas present themselves as fairly well circumscribed rather soft, usually intracutaneous tumors over which the epidermis is normal

but highly malignant fibrosarcomas may possess little or no collagen. Instead, on staining with a reticulum stain, they are seen to contain numerous reticulum fibers (Foot).

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atypicality of the cells favor a diagnosis of myxosarcoma The cells tend to be stellate and multipolar

SYNOVIAL CYST OF THE SKIN (MYXOMATOUS DEGENERATION CYST OF THE SKIN)

This lesion occurs most commonly on the hands particularly near the terminal interphalangeal joints The lesion consists of a small semiglobular translucent tumor surrounded by erythema When punctured a clear mucinous fluid exudes

Histopathology Histologic examination reveals a cystic cavity in the dermis or the subcutaneous tissue The lining wall is made up of fibrous tissue and shows no endothelial or epithelial lining The cyst is filled with mucoid material

The histogenesis is not clear Mackee and Andrews regarded the lesion as a synovial cyst Savatard held that the lesion formed because of mucoid degeneration of a fibroma Woodburne stated that he had never seen any evidence of a previously existing solid tumor He expressed the belief that the lesion arises because of myxomatous degeneration of fibrous tissue of the dermis or of other fibrous tissue

3 TUMORS OF FATTY TISSUE

LIPOMA

Lipomas occur as single or multiple subcutaneous soft rounded lobulated growths which may or may not be movable against the overlying skin In rare instances multiple lipomas have been reported as present not only in the subcutaneous but also in the visceral fat depots This condition is known as systemic multicentric lipoblastosis (Tedeschi)

Histopathology Lipomas are composed of fat cells and may or may not be surrounded by a connective tissue capsule The fat cells in lipomas usually do not differ from normal fat cells Occasionally they are slightly larger In some lipomas there is more in others less of a connective tissue framework than in normal subcutaneous fat Those containing a considerable proportion of connective tissue are called fibrolipomas

Systemic multicentric lipoblastosis shows not only adult fat cells as lipomas do but also embryonal fat cells and undifferentiated mesenchymal cells with all intermediate stages These lesions are hamartomas analogous to the lesions of von Recklinghausen s disease and not sarcomas They show no cellular disorder and no mitotic figures (Tedeschi)

Histopathology. Myxomas contain embryonal fibroblasts that possess the ability to produce mucin in a manner similar to that of the embryonal fibroblasts of the umbilical cord The number of these cells in myxomas is usually small Those present are spindle shaped or stellate cells possessing multipolar processes The stroma appears homogeneous and gelatinous It stains pale blue with hematoxylin



Fig 218 Myxoma The stroma appears homogeneous and in some places gelatinous The empty spaces are caused by shrinkage of the mucin in the process of fixation (×200)

and eosin, and red with Best s mucicarmine stain Because of shrinkage in the process of fixation empty cleftlike spaces frequently are observed in the stroma (Fig 218)

Many myxomas are not pure but contain other mesodermal elements Thus fibromyxomas and lipomyxomas occur

MYXOSARCOMA

Clinically, myxosarcomas are as a rule primarily subcutaneous tumors which, as they grow in size may cause ulceration of the skin

Histopathology. A decision whether a tumor represents a myxoma or a myxosarcoma is often difficult A high degree of cellularity and

cytoplasm (Fig 219) There is a loose meshwork of connective tissue which usually but not always is mucoid (Stout)

A highly malignant liposarcoma contains highly atypical lipoblasts with bizarre nuclei The amount of fat in them is often small There are areas which resemble fibrosarcoma The stroma usually is mucoid

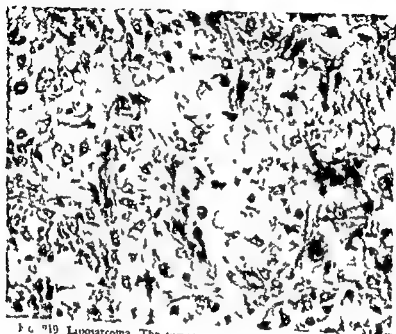


Fig 219 Liposarcoma The tumor is composed of ...

MALIGNANT HIBERNOMA

The clinical appearance of malignant hibernoma is the same as that of other liposarcomas

Histopathology The cells comprising this tumor are rounded, have a centrally placed nucleus and contain numerous small and large vacuoles of fat in their cytoplasm Those containing large vacuoles are called mulberry cells. Some of the cells are of very large size and contain multiple bizarre nuclei (Fig 220) The ... tumor ...

Com

HIBERNOMA

Hibernoma is a rare, benign, solitary, soft, subcutaneous tumor which may slowly increase in size Clinically, it is indistinguishable from lipoma

Histopathology. The tumor is composed largely of multilocular fat cells which resemble those occurring as brown fat in the hiber nating gland of hibernating animals However, since multilocular fat cells resembling those of brown fat may occur as a transitory phase in the maturation of ordinary, yellow adipose tissue, it is possible that hibernoma merely represents a tumor of embryonal yellow fat cells (Sutherland)

Histologic examination reveals a lobulated tumor composed pre dominantly of closely spaced, round or oval cells with a distinct cell membrane and centrally placed nucleus The cells contain either granules or small vacuoles or locules which stain positive with fat stains This fat is in contrast with mature fat, doubly refractile to polarized light (Sutherland) In some multilocular cells coalescence of smaller into larger locules can be seen, with eccentric displacement of the nucleus There are, in addition a few unilocular, normal ma ture fat cells which are larger than the granular and multilocular cells There thus seems to be evidence of a transition from granular to multilocular and even to unilocular fat cells (Brines and Johnson)

Differential Diagnosis. The tumor can be differentiated from ma lignant hibernoma by its regular architecture and the absence of mitotic figures and multinucleated cells

LIPOSARCOMA

Liposarcomas as a rule arise as such but they may *develop* within a pre existing lipoma (Sternberg) They not only occur in the sub cutaneous fat but also may be found wherever there is fatty tissue Those located in the subcutaneous fat present themselves as diffuse nodular *infiltrations Metastases are common, especially* to the lungs and the liver

Histopathology. The histologic picture varies somewhat with the degree of malignancy Moderately malignant tumors are easily recog nizable as fatty tumors, while very malignant ones may not be identi fiable as such unless fat stains are employed

A moderately malignant liposarcoma consists of adult fat cells and moderately atypical immature fat cells (lipoblasts) The latter have a spindle shaped or stellate nucleus and contain fat droplets in their

appear cut in transverse and others in longitudinal direction (Fig 221) Each nerve bundle is surrounded by fibrous tissue



Fig 221 Neuroma Numerous thick bundles of medullated nerves are present Each nerve bundle is surrounded by fibrous tissue (×900)

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Neurofibromatosis is characterized by the presence of multiple cutaneous tumors which possess a characteristic soft consistency and usually are flesh-colored but may be brownish or violaceous The lesions are semiglobular or pedunculated and vary considerably in size Occasionally large pendulous flabby masses weighing a pound or more are encountered In most cases in addition to the tumors the skin shows yellowish brown pigmented macules of various size and shape—so-called café au lait spots

Histogenesis Neurofibromas are tumors of nerve sheaths Normally each neurite or axon whether myelinated or not, is surrounded by a neuro-ectodermal sheath the schwannian sheath, and

Stout regards this as evidence that ordinary adipose tissue and brown fat come from the same ancestral lipoblastic cell

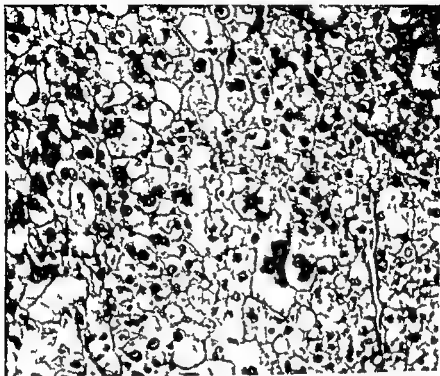


Fig 290 Malignant hibernoma The fat cells contain bizarre nuclei and are filled with small and large vacuoles of fat Those containing large vacuoles are called mulberry cells There is hardly any stroma (×200)

4 TUMORS OF NERVE TISSUE

Three types of nerve tumors may occur in the skin neuroma neurofibroma and neurolemoma

NEUROMA

Neuromas nearly always occur as single tumors secondary to an injury of a nerve In rare instances they occur as single (Duemling) or multiple (Ludy) tumors apparently without preceding nerve injury Neuromas are small reddish nodules which may or may not be painful

Histopathology In their histologic appearance neuromas resemble the amputation neuromas which represent a hyperplasia of nerves and are not tumors For this reason Ludy preferred to regard also the nontraumatic neuromas of the skin as neuromatoid hyperplasia

Neuromas show numerous thick bundles of medullated nerves in the dermis extending in different directions Thus some bundles

It is unfortunate that the schwannian cell and the endoneurial fibroblast cannot be differentiated by present histologic methods Since the schwannian cell can also produce reticulum fibers and col lagen (Masson, Murray and Stout) the presence of these structures in neurofibromas does not decide the issue Murray and Stout believe that their findings in tissue cultures favor the schwannian origin of



Fig 223 Neurofibroma (von Recklinghausen's disease) *In this tumor mucoid degeneration of the collagen* has taken place *This is a not uncommon occurrence in lesions of* neurofibroma (×200)

neurofibroma because the mode of outgrowth of schwannian cells from normal nerves and of cells in neurofibroma is very *similar*

Histopathology Histologic examination of the cutaneous tumors shows them to be *well circumscribed* but not encapsulated The tumor masses often extend into the subcutaneous fat They are com posed of *wavy fibrils which lie in loose strands and* tend to form eddies and whorls The loose *textured* wavy arrangement of the fibrils is characteristic of neurofibroma (*Fig* 222) With hematoxylin

finds a fairly large number of nuclei which are oval or spindle shaped,

a mesodermal sheath, the endoneurium (see page 22). It is still a matter of controversy whether the cells composing neurofibromas represent neuro ectodermal schwannian cells or mesodermal endoneurial cells. Whereas von Recklinghausen originally regarded the tumors as derived from the connective tissue of nerves, Verocay, in 1910, first suggested that the cells of the tumors were immature cells

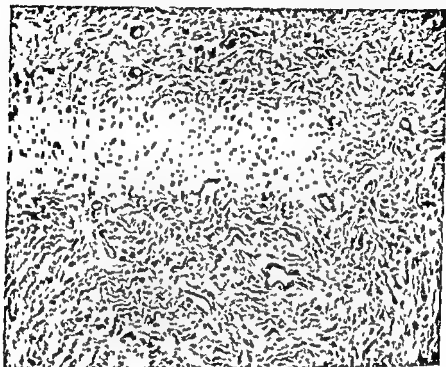


Fig 222 Neur ... P ... d cease) The tumor is composed of ... gether and tend ... pale blue with hematoxylin eosin (×200)

of the sheath of Schwann and thus neuro ectodermal cells He suggested that the tumors be called neurinomas Among more recent writers on the subject, some (Murray and Stout) subscribe to Verocay's view. Others (Penfield, Tarlov) still adhere to the view that the tumors develop from the perineural connective tissue Many more recent authors however, feel that probably both ectodermal

ery) Masson, who observed that neural elements were conspicu in young tumors but sparse or absent in old tumors concluded that neurofibromas basically were neural tumors However, with aging, the neural elements gradually degenerated and were replaced by connective tissue proliferation.

nervous systems and of the bones, however, it is a not uncommon occurrence Hosoi, in 1931, found 65 instances of malignant degeneration reported in the literature; he stated that this represented 13 per cent of all the reported cases of neurofibromas The conclusion drawn by Charache that 'sarcomatous transformation is present in 13 per cent of all cases of multiple neurofibroma" is not justified, however, because in neurofibromatosis, as in other common diseases,

fibroma In some, however, the pattern of a neurofibroma is preserved there is still a wavy arrangement of the collagen fibrils, but the nuclei are increased in number and are atypical (Fig 224) Nerve fibers are never found (Stout, Wachstein and Wolf)

NEUROLEMOMA

Neurolemoma occurs as either solitary or multiple tumors but not as a systematized disease like neurofibromatosis The lesions which are asymptomatic are found in the dermis or in the subcutaneous tissue They can reach a diameter of several centimeters and undergo

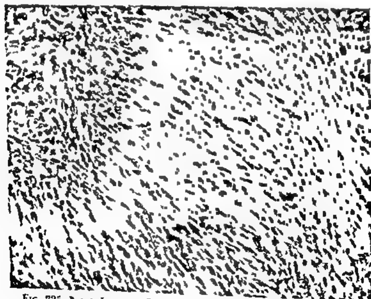


Fig 225 Neurolemoma Numerous elongated nuclei are arranged in a streaming fashion In the center of the field lies a so-called Verocay body formed by a double palisade of nuclei enclosing a space nearly devoid of nuclei (X200)

uniform in size and rather pale staining Elastic fibers are absent in the tumors On staining with Foot s stain numerous wavy reticulum fibers are seen In most neurofibromas a few nonmedullated thin long nerve fibers can be recognized on staining with special nerve stains, such as Bodian s stain (McNairy and Montgomery)

Not infrequently mucoid degeneration of the collagen is observed in parts of a tumor or in an entire tumor In such cases the nuclei

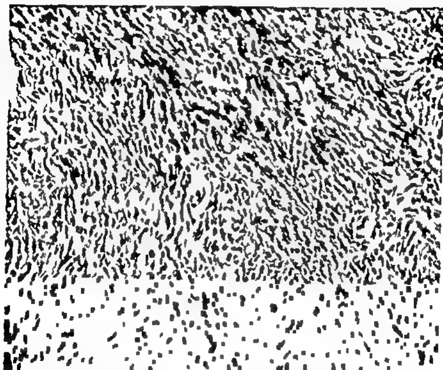


FIG 224 Neurofibrosarcoma (von Recklinghausen s disease) The wavy pattern characteristic of neurofibroma is preserved but the nuclei are increased in number and are atypical (×200)

are embedded in a homogeneous pale blue ground substance (Fig 223) One must be familiar with this change because it results in a histologic picture quite different from that usually associated with neurofibroma

The pigmented *macular lesions seen in neurofibromatosis* the so called cafe au lait spots merely show increased melanin pigmentation *in the* basal layer

Systemic Lesions There may be tumors of the central and peripheral nervous systems of the viscera (Grill and Kuzma) and of the bones Involvement of a bone may lead either to extensive destruction or to hypertrophy of bony tissue (Westcott and Ackerman)

Malignant Degeneration Malignant degeneration of neurofibromas of the skin is rare In tumors of the central and the peripheral

Nevus flammeus is characterized by one or several dull red or bluish red patches of irregular outline, not elevated above the level of the skin

Nevus vasculosus is a raised, bright red, soft, often lobulated tumor. When lobulated, its appearance resembles that of a strawberry.

Cavernous hemangioma consists of a large, soft, subcutaneous mass If, as is often the case, the lesion is located on the face, consid-



lated capillaries with considerable proliferation of their endothelial cells (×100)

erable deformity may result The overlying skin may be normal

cells is present (Fig 226)

NEVUS VASCULOSUS, which represents a capillary hemangioma, addition

cons

prol

around capillary lumina In addition, they form solid strands and masses with little evidence of vascular lumina

CAVERNOUS HEMANGIOMA shows in the lower dermis and in the subcutaneous tissue large, irregular spaces filled with blood. They

partial cystic degeneration. Malignant degeneration does not occur, however.

Histopathology. The tumor arises from the sheath of Schwann of a peripheral nerve and is composed of schwannian cells. It is well encapsulated. One observes numerous bands of closely spaced, elongated nuclei arranged in a twisting, streaming fashion. Here and there, the nuclei lie in two rows or palisades enclosing a space nearly devoid of nuclei. Such formations are called Verocay bodies (Fig. 225). In addition to these areas of streaming and palisading, there are areas in which the schwannian cells are embedded in a loose meshwork of fine connective tissue fibers. Small cysts may be present which by coalescence may form gross cystic spaces (Stout). No nerve fibers are found in neurolemoma. Mast cells often are present in conspicuous numbers.

5. TUMORS OF VASCULAR TISSUE

HEMANGIOMA

Hemangiomas may be divided into three clinical types: (1) nevus flammeus (port wine nevus), (2) nevus vasculosus (strawberry mark) and (3) angioma cavernosum.



Fig. 226. Hemangioma (nevus flammeus). The capillaries are increased in number. They are dilated, engorged with blood and lined by only a single layer of endothelial cells. (×100)

Nevus flammeus is characterized by [illegible] or [illegible] bluish red patches of irregular outline, [illegible] above the level of the skin.

Nevus vasculosus is a raised, bright red, [illegible] tumor. When lobulated, its appearance resembles that of a strawberry.

Cavernous hemangioma consists of a [illegible] mass. If, as is often the case, the lesion is located on the face, considerable deformity may result. The overlying [illegible]



Fig. 227 Hemangioma (nevus vasculosus). There are numerous dilated capillaries with considerable proliferation of their endothelial cells. (×100)

[illegible]

Nevus vasculosus, which represents a capillary [illegible] in addition to [illegible]

[illegible] masses with little evidence of vascular lumina [illegible] they form solid strands and

Cavernous hemangioma shows in the lower dermis and in the subcutaneous tissue large, irregular spaces filled with blood. They

are lined by a single layer of thin endothelial cells and by thick walls (Fig. 228). The thickening is produced mainly by overgrowth of adventitial cells

Sclerosing hemangioma, since it is a dermatofibroma rather than an angioma, is discussed under "Dermatofibroma" (see page 403)



Fig 228 Hemangioma (hemangioma cavernosum). The blood vessels show considerable thickening of their walls produced by overgrowth of adventitial cells (×100)

GRANULOMA PYOGENICUM

This lesion, which usually is single, consists of a dull red, soft or fleshy, raised, more or less pedunculated nodule Its size varies from 0 5 to 2 cm in diameter The surface may show a smooth, atrophic epidermis but often is covered by crusts The lesion bleeds easily when traumatized

Histopathology. On histologic examination, one finds a circumscribed, raised, pedunculated lesion covered by a flattened epidermis and containing numerous newly formed capillaries showing varying

degrees of dilatation (Fig 229) A slight to moderate amount of endothelial proliferation is usually present The capillaries are embedded in a loose, edematous occasionally mucoid connective tissue At the neck of the pedunculated lesion the epidermis usually shows acanthotic inward growth thus forming a so called epidermal collarette



Granuloma pyogenicum The lesion is pedunculated It is composed of numerous capillaries embedded in a loose edematous stroma No inflammatory reaction is present (X50)

In early lesions one finds no inflammatory reaction (Freund) In older lesions because of the fact that the thinned epidermis usually erodes secondary inflammatory changes are often present in the stroma and may give the tumor a granulomatous appearance

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of the raised pedunculated growth of the lesion, the presence of edema or mucoid degeneration in the stroma, the thinning of the epidermis over the tumor and the collarette formation of the epidermis at the neck of the tumor

ANGIOKERATOMA MIBELLI, ANGIOKERATOMA CORPORIS DIFFUSUM

In angiokeratoma Mibelli, one observes on the dorsum of the fingers, on the toes and on the knees from pinhead to bean sized dark-red, vascular papules with a verrucous surface The disease arises in young subjects

In angiokeratoma corporis diffusum, dark red, vascular papules are present in great number over the entire trunk They are smaller and show less hyperkeratosis than those of angiokeratoma Mibelli *Angiokeratoma corporis diffusum may be associated with internal lesions* such as swelling and vacuolation of the muscle fibers of the blood vessels and of the heart (Ruiter)

Histopathology. Histologic examination of the cutaneous lesions reveals in both diseases telangiectasias of superficial location associated with changes in the epidermis consisting of hyperkeratosis, acanthosis, irregular proliferation of the rete ridges and papillomatosis Greatly dilated capillaries lined by a thin layer of endothelial cells lie in the papillae and are partly or completely surrounded by the hypertrophic stratum malpighii If completely surrounded, the dilated capillaries have the appearance of intra epidermal "blood cysts" *Some of the blood cysts may have lost their endothelial lining* Atrophy of the stratum malpighii may occur directly over blood cysts because of the pressure which the cysts exert on the overlying epidermis

SENILE HEMANGIOMA

Senile hemangiomas are small, raised soft, dark red nodules, measuring usually between 1 and 3 mm in diameter They may be present in large numbers in persons past middle life Their sites of predilection are the face and the upper trunk

Histopathology. Senile hemangiomas, within a circumscribed area of the upper dermis show numerous dilated capillaries lined by a single layer of endothelium The epidermis shows flattening of the rete ridges (Beek) Occasionally however they may show acanthosis as well as hyperkeratosis and even inclusion of dilated capillaries into the epidermis In that case histologic distinction from angiokeratoma may be impossible (Traub and Tolmach)

NEVUS ARANEUS

Nevus araneus or spider nevus is characterized by a central slightly elevated red dot from which fine blood vessels radiate. Occasionally pulsation can be observed. Spider nevi are common on the upper half of the face.

Histopathology. According to Walsh and Becker, nevus araneus represents a small arteriovenous anastomosis. They concluded from serial sections that in this lesion an arteriole ascends high into the dermis where it changes directly into a vein. The vein divides into a network of smaller venules. The latter give the lesion its spiderlike appearance clinically.

Ho ... differ in their composition ... pes of vascular arrangements ... al vessel of the "spider nevus" to be an artery which branched successively into arterioles and capillaries. In the other type, the so-called glomus type, they found the afferent artery to be connected with the central vessel of the "spider nevus" by a short junction which had the histologic appearance of the Sucquet-Hoyer canal as seen in the cutaneous glomus. In contrast with the usual glomus, however, the central vessel of the "spider nevus" was not a collecting vein but continued into capillaries.

OSLER'S DISEASE (FAMILIAL HEMORRHAGIC TELANGIECTASIA)

This familial disease is characterized by the presence of numerous telangiectases on the skin and the mucous membranes. The presence of telangiectases on the mucous membranes may result in hemorrhages from the nose, the mouth, the stomach, the kidney, the rectum or the vagina.

Histopathology. Scattered greatly dilated capillaries are present in the upper dermis. Fingerland and Janousek noted that the venules in the lower dermis showed narrowing of their lumina and an increase in the number of adventitial cells.

LYMPHANGIOMA

A superficial and a deep variety of lymphangioma exist. The superficial variety, lymphangioma circumscriptum, is characterized by the presence of groups of small, thick-walled vesicles resembling frog's spawn. Some of the vesicles may show a verrucous surface.

The deep variety, lymphangioma cavernosum, causes diffuse en

of the raised pedunculated growth of the lesion, the presence of edema or mucoid degeneration in the stroma, the thinning of the epidermis over the tumor and the collarette formation of the epidermis at the neck of the tumor

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GLOMUS TUMOR

This tumor usually occurs as a single small, deep seated pink or purplish nodule which is tender and gives rise to severe paroxysmal pains In rare instances there are numerous lesions in which case tenderness is absent in most of them (Weidman and Wise, Eyster and Montgomery) The most common sites of the solitary lesions are

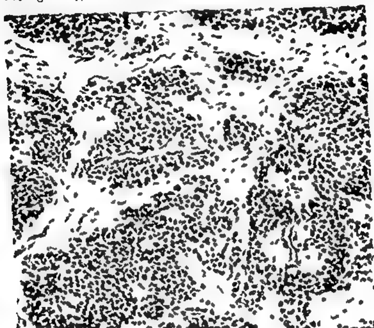


Fig 231 Glo[illegible]

[illegible] a central vessel (×200)

the nail bed and the fingertips however, the lesions may occur elsewhere

Histopathology The glomus tumor represents a benign tumor of the cutaneous glomus a structure composed of an arterial segment the Sucquet Hoyer canal and a venous segment The normal Sucquet Hoyer canal possesses a narrow lumen lined with a single layer of endothelial cells and a thick mantle of glomus cells (see page 24) Glomus cells have a faintly eosinophilic cytoplasm and [illegible]
pale [illegible]
ep[illegible]
fi[illegible]

A glomus tumor is composed of vascular lumina and numerous

largement of the affected region for instance macrocheilia and macroglossia

Histopathology In lymphangioma circumscriptum one observes in the uppermost portion of the dermis cystically dilated lymph vessels lined by a single layer of endothelium (Fig 230) They contain



Fig 230 Lymphangioma circumscriptum Cystically dilated lymph vessels lined by a single layer of endothelial cells are present in the upper dermis The epidermis shows downward growth and more or less surrounds some of the lymph vessels There is moderate hyperkeratosis (×50)

coagulated lymph and lymphocytes The stratum malpighii varies greatly in thickness Over some of the lymph cysts it is thinned elsewhere it may show considerable acanthosis and irregular downward growth Some of the dilated lymph vessels may be completely surrounded by epidermis Hyperkeratosis is common The histologic picture may be similar to that of angiokeratoma except that the dilated areas contain lymph fluid instead of blood

In lymphangioma cavernosum large lymph filled cystic spaces lined by a single layer of endothelium are present in the dermis and the subcutaneous tissue There is concomitant hypertrophy of the connective tissue

GLOMUS TUMOR

... small deep seated pink or ... paroxysmal pu ... which case pains ... tenderness is absent in most of them (Weidman and Wise, Eyster and Montgomery) The most common sites of the solitary lesions are



FIG 231 Glomus tumor There are numerous vascular lumina of varying size lined by a single layer of endothelial cells and surrounded by proliferating rows of glomus cells However some of the masses of glomus cells do not show a central vessel (×200)

the nail bed and the fingertips however the lesions may occur elsewhere

Histopathology The glomus tumor represents a benign tumor of the cutaneous glomus a structure composed of an arterial segment the Sucquet Hoyer canal and a venous segment The normal Sucquet Hoyer canal possesses a narrow lumen lined with a single layer of endothelial cells and a thick mantle of glomus cells (see page 24) Glomus cells have a faintly eosinophilic cytoplasm and large, oval pale nuclei with a distinct chromatin structure. Thus they resemble epithelioid cells They are richly supplied with nonmyelinated nerve fibrils

A glomus tumor is composed of vascular lumina and numerous

glomus cells As a rule the lumina are small but sometimes especially in those cases with multiple lesions, the lumina are of considerable size (Weidman and Wise, Eyster and Montgomery) The vascular lumina are lined by a single layer of flattened endothelial cells and usually, by several layers of glomus cells (Fig 231) Some of the vessels closely resemble the *Sucquet Hoyer canals of the normal* glomus In many areas the glomus cells proliferate irregularly from the vascular walls into the connective tissue stroma of the tumor In addition masses of glomus cells without central lumina and scattered glomus cells are present in the stroma

The connective tissue stroma of the tumor is loose, edematous and contains scattered fibroblasts and glomus cells It may show marked mucoid degeneration Special staining for nerve fibers (Bodian stain) will reveal numerous nerve fibers most of them nonmyelinated They show considerable branching and terminate as fine fibrils around the glomus cells

HEMANGIOPERICYTOMA

This rare tumor may arise wherever there are capillaries Its most common sites are the skin and the subcutaneous tissue Hemangio

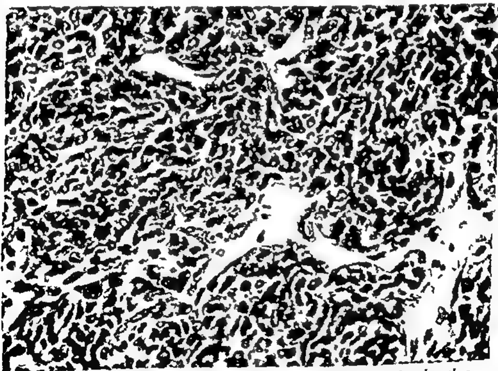


FIG 232 Hemangiopericytoma The capillary lumina are lined with a single layer of endothelial cells and are surrounded by irregularly proliferating closely packed pericytes Most of the pericytes are spindle shaped (×400)

pericytomas have no diagnostic clinical appearance They are of varying size firm and nodular Some are benign some are gradually growing and some even metastasize

Histopathology The tumor is characterized by the presence of endothelial tubes and sprouts surrounded by irregularly proliferat

In some cases the pericytes show frequent mitotic figures and invasion into vascular lumina so that the tumor must be regarded as malignant or at least potentially malignant (Fisher Kaufman and Mason) In one instance widespread metastases resulting in death have been reported (Forrester and Houston)

in the glomus tumor show a more orderly arrangement and are more uniform in appearance being round to oval and never spindle shaped

KAPOSI S SARCOMA (MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA)

Kaposi s sarcoma consists of an *eruption of multiple bluish red or dark brown nodules and plaques The lesions not infrequently show a verrucous surface They may undergo ulceration* Spontaneous involution of some of the lesions occurs occasionally The sites of predilection are the distal portions of the extremities but other areas of the skin may also become involved

Visceral lesions occur in about 10 per cent of the cases (Tedeschi Folsom and Carnicelli) *The most frequent sites are* in order of frequency the *gastro-intestinal tract the liver* the *lungs* and the retroperitoneal and the *mesenteric lymph nodes* (Dorffel) In rare instances there may be visceral lesions of Kaposi s sarcoma without cutaneous involvement (Tedeschi Folsom and Carnicelli)

Histogenesis The histogenesis of Kaposi s sarcoma is not fully ascertained A widely accepted view (with which the author agrees) is that *Kaposi s sarcoma is a benign angiomatosis* arising from embryonal vascular cells and that the lesions are autochthonous in origin rather than metastatic (Gilchrist and Ketron Lang and Hasl

hofer, Becker and Thatcher Tedeschi, Folsom and Carnicelli) Dissenting views are held by Pautrier and Diss who regard Kaposi's sarcoma as a neurov Dorffel, who regards it as a disease of the and related to the lymphoma group of disease is a sarcoma proposed originally by Kaposi has been abandoned by most writers



Fig 233 Kaposi's sarcoma early granulomatous stage The capillaries are increased in size and number Their endothelial cells are large A diffuse chronic inflammatory infiltrate is present In the lower central section of the illustration one can see groups of endothelial cells attempting to form new blood vessels (×200)

Nevertheless some authors (Aegerter and Peale, Sachs Azulay and Convit) still maintain that it represents a sarcoma

Evidence against the concept of Kaposi's sarcoma as sarcoma and in favor of the autochthonous rather than the metastatic origin of the lesions are (1) the absence of a primary focus that progressively enlarges, (2) the appearance of widely separated lesions in crops (3) the spontaneous regression of some lesions and (4) the fact that histologic examination may reveal very early stages of development in late appearing lesions Occasionally however a lesion may undergo malignant degeneration and then grow as a true sarcoma and cause metastases

Fig 234 Kaposi's sarcoma neoplastic stage On the left the neoplasia is fibroblastic on the right it is angiomatous (×100)



Fig 235 Kaposi's sarcoma angiomatous lesion There are numerous vascular lumina Most lumina are lined by only a single layer of endothelial cells but some are surrounded also by perithelial cells The stroma is edematous and contains extravasated erythrocytes (×200)

hofer, Becker and Thatcher, Tedeschi, Tolsom and Carnicelli). Dissenting views are held by Pautrier and Diss, who regard Kaposi's sarcoma as a neurovascular dysgenesis, and by Dorffel, who regards it as a disease of the reticulo-endothelial system and related to the lymphoma group of diseases. The idea that the disease is a sarcoma, proposed originally by Kaposi, has been abandoned by most writers.



FIG. 238. Kaposi's sarcoma, early granulomatous stage. The capillaries are increased in size and number. Their endothelial cells are large. A diffuse chronic inflammatory infiltrate is present. In the lower central section of the illustration one can see groups of endothelial cells attempting to form new blood vessels. (×900)

Nevertheless, some authors (Aegerter and Peale, Sachs, Azulay and Convit) still maintain that it represents a sarcoma.

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20 reticulum represents young collagen) In old regressing lesions one may find considerable collagenization due to maturation of the young fibroblasts *This may lead eventually to fibrosis* cicatrization and disappearance of the lesion

If malignant degeneration occurs in a lesion of Kaposi s sarcoma the resulting sarcoma is indistinguishable from fibrosarcoma

Seven instances are recorded in the literature in which lymphoma occurred in patients with Kaposi s sarcoma In four of these patients lymphocytic lymphoma was present (Cole and Crump Hufnagel and Dupont Sachs and Gray Fischer and Cohen) in two mycosis fungoides (Lane and Greenwood Winer) and in one Hodgkin s disease (Greenstein and Consten) There is not sufficient proof that Kaposi s sarcoma and lymphoma are related It is *therefore*, best to regard their coexistence as accidental

HEMANGIO ENDOTHELIOMA (HEMANGIOSARCOMA)

Malignant tumors arising from blood vessels are rare According to the two types of cells of which capillaries are composed perithelial cells and endothelial cells two types occur hemangio fibrosarcoma and hemangio endothelioma

Hemangio fibrosarcomas have the histologic appearance of fibrosarcomas with conspicuous capillary proliferation and may therefore be regarded as fibrosarcomas The sarcomas which occasionally arise *in lesions* of Kaposi s sarcoma are of that type This leaves hemangio endothelioma as the only specific malignant tumor arising from blood vessels

Hemangio endothelioma usually occurs as a diffusely infiltrating mass which is soft dark red and raised above the surface of the skin It grows slowly but progressively and may attain large size Metastases occur

Hist is characterized (1) by the pr greater numbers than required to line the vessels with a simple endothelial membrane and (2) by the new formation of vascular tubes with a marked tendency for their lumina to anastomose (Stout)

The number of vascular lumina varies in different tumors but as a rule vascular lumina are numerous They are irregular in size and shape Large tortuous sinuses may be present (Fig 236) The vascular channels are lined by large, atypical endothelial cells In many areas endothelial cells lie in several layers and proliferate into the lumina to such a degree that the vascular tubes are completely obscured and cannot be made out as such when routine stains are used When however a reticulum stain is used the outline of the vessels

Histopathology. The two types of cells of which capillaries are composed participate in the formation of the lesions endothelial and perithelial cells The perithelial cell is a pericapillary histiocyte which may develop into a fibroblast (see page 33) In addition an inflammatory reaction is observed in early lesions One may divide the lesions of Kaposi s sarcoma into early granulomatous lesions and late neoplastic lesions The latter may be either "angiomatous," if endothelial cell proliferation predominates, or "fibroblastic" if perithelial cell proliferation predominates

In early granulomatous lesions, the blood vessels of the dermis are dilated and increased in number (Fig 233) Their endothelial cells are swollen There is perivascular as well as diffuse cellular infiltration, varying in severity The infiltrate is composed of lymphocytes, plasma cells and some histiocytes and fibroblasts One may see groups of endothelial cells attempting to form new blood vessels Frequently, one sees small groups of extravasated erythrocytes and deposits of hemosiderin The histologic picture in the early stage is not always diagnostic, however, the presence of extravasated erythrocytes and of hemosiderin in a granulomatous lesion as described above should always make one think of early Kaposi s sarcoma

In late lesions, the histologic picture may be either angiomatous or fibroblastic, frequently both phases are found intermingled in the same lesion (Fig 234) In angiomatous lesions one finds numerous vascular lumina They vary greatly in size and occasionally are saccular Most lumina show only a single layer of swollen endothelial cells, but some are surrounded, in addition, by perithelial cells (Fig 235) The stroma in which the vessels are embedded often is edematous and usually contains hemorrhages and hemosiderin deposits

In fibroblastic lesions, one observes marked proliferation of spindle shaped cells which represent young fibroblasts (Symmers) and are derived from perithelial cells They lie in strands which extend irregularly in all directions The nuclei vary in size and staining qualities and some of them are atypical Mitotic figures are present though usually in small number The histologic picture is thus very much like that of a fibrosarcoma One feature however, distinguishes the fibroblastic lesions of Kaposi s sarcoma from fibrosarcoma and that is the presence of small or large groups of extravasated erythrocytes and of granules of hemosiderin between the fibroblasts This feature sometimes is not conspicuous but a thorough search or staining for iron almost invariably will reveal such areas (see Plate 3) The fibroblasts, being immature, form only little collagen as a rule but staining with Foot s stain will reveal a rather dense network of reticulum fibers produced by them (Symmers) (As discussed on page

can be seen In some tumors, one may see endothelial cells extend as invading cords between the fibers of the connective tissue and, occasionally, they may occur in large, solid sheets

The endothelial cells seen in this tumor are large and polyhedral and have a well-defined cellular membrane and relatively clear cytoplasm (Fig 237) The nuclei tend to be round to oval, pale and vesicular However, many nuclei are atypical, being irregular in shape and hyperchromatic In addition, numerous mitotic figures are usually present Some of the endothelial cells are multinucleated

POST MASTECTOMY LYMPHANGIO SARCOMA

Lymphangio sarcoma may occur in post mastectomy lymphedema (Stewart and Treves) Several years after radical mastectomy for carcinoma, subcutaneous and cutaneous nodules appear in the edematous tissue of the arm on the side of the operation The cutaneous nodules have a bluish color The clinical resemblance to Kaposi's sarcoma may be great The nodules are not radio sensitive Metastases especially to the lungs, occur

Histopathology. The nodules are composed of large, atypical cells which, in some places form solid proliferations and, in others, produce capillary vessels and lacunar structures The lumens are usually empty, but, in some cases, contain occasional accumulations of red blood cells In such cases, the tumor represents a mixed lymphangio and hemangio-endothelioma (Jessner Zak and Rein) Outside the tumor formations, one observes numerous dilated, proliferating lymphatics in the dermis in the subcutaneous tissue and even deeper, in the intermuscular fascia

Differential Diagnosis. The resemblance to hemangio endothelioma is so great that differentiation is impossible except perhaps on the basis of the amount of red blood cells in the lumina The tumor differs from Kaposi s sarcoma by the intralymphatic proliferation and greater atypicality of the endothelial cells and by the absence of atypical fibroblastic formations

6 TUMORS OF MUSCULAR TISSUE

LEIOMYOMA

There are three types of leiomyoma of the skin (1) multiple cutaneous leiomyomas (2) solitary angioleiomyomas and (3) solitary genital leiomyomas (myomes dartoiques).

Multiple cutaneous leiomyomas are from pinhead- to pea sized, brown or bluish, firm elevated nodules which tend to occur either

Fig 236 Hemangioendothelioma Low magnification There are numerous vascular lumina on the right side is a large vascular sinus The vascular channels are lined by large atypical endothelial cells which in some areas proliferate irregularly into the lumina (×100)

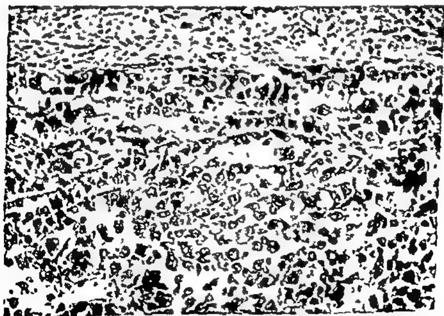


Fig 237 Hemangioendothelioma High magnification of Figure 236 A large sinus is shown into which atypical endothelial cells proliferate Some of the endothelial cells are multinucleated (×200)

muscle of veins and genital leiomyomas from either the muscularis sexualis or the muscularis mamillae (Stout)

All leiomyomas are composed of interlacing bundles of smooth muscle fibers (Fig 239) Proliferating collagen bundles are often intermingled with the smooth muscle bundles The muscle fibers composing the bundles are straight or slightly wavy and contain centrally located thin very long blunt edged nuclei The muscle bun



... is present within a leiomyoma The muscle bundles of the vein merge with those of the tumor (×200)

... aniline blue stain may be used With th...

... only few blood vessels

Solitary angioleiomyomas lie largely in the subcutaneous tissue, are encapsulated and contain large blood vessels, probably veins, with thick muscular walls (Fig 239) Some of these vessels have a stellate lumen because of contraction of the muscular tissue In some areas, one sees the muscle bundles of the vessels merge with those of the tumor (Jansen)

Solitary ...
not encaps...
a rather la...

on the back the face or the extensor surfaces of the extremities and usually are arranged in groups They often are painful and sensitive to pressure

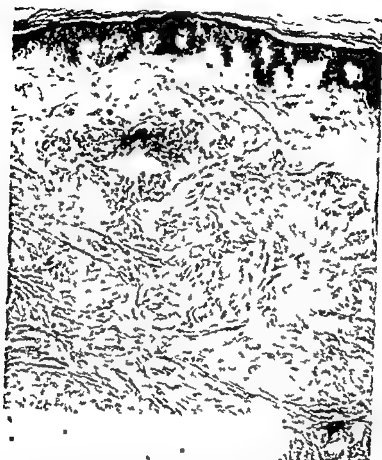


Fig 238 Leiomyoma nonvascular type The tumor is composed of interlacing bundles of smooth muscle fibers The nuclei of the smooth muscle fibers are thin long and blunt edged Collagen bundles are intermingled with the smooth muscle bundles Both stain alike with hematoxylin eosin To differentiate them an aniline blue stain may be used (See Plate 4) (×100)

Solitary angioleiomyomas usually are subcutaneous in location but are adherent to the overlying skin They rarely grow larger than 1 cm in diameter and usually are nontender

Solitary genital leiomyomas are located either on the scrotum the labia majora or rarely on the nipples They may attain considerable size several centimeters in diameter and are nontender

Histopathology Multiple cutaneous leiomyomas arise from the arrectores pilorum muscles solitary angioleiomyomas from the smooth

uently, shows active downward proliferation, even with horn pearl ormation (Fig 241) (Bloom and Gintler) This pseudo epithelioma ous hyperplasia has been mistaken for squamous cell carcinoma in everal cases reported in the literature (Eickhoff)



... epithelium shows pseudo-epitheliomatous hyperplasia The dermis contains numerous large pale cells as they are typical of this tumor (×200)

In lesions of the tongue one not infrequently sees areas suggesting transitions between the *tumor* cells and *mature* muscle fibers (Crane and Tremblay) This observation has been the reason that granular cell myoblastomas were at first generally regarded as tumors of immature striated muscle cells (myoblasts) However, in recent years, several authors have expressed the view that these transitions were only apparent and that granular-cell myoblastomas were composed of either schwannian cells or endoneural fibroblasts and thus were of neural origin (Fust and Custer, Ashburn and Rodger, Bangle)

GRANULAR-CELL MYOBLASTOMA

Granular-cell myoblastomas are solitary tumors occurring most commonly in the tongue, the skin and the subcutaneous tissue (Crane and Tremblay). They usually are benign, but malignant degeneration occurs occasionally (Ross, Miller and Foote). Cutaneous myoblastomas usually consist of a firm, round, well-circumscribed, non-

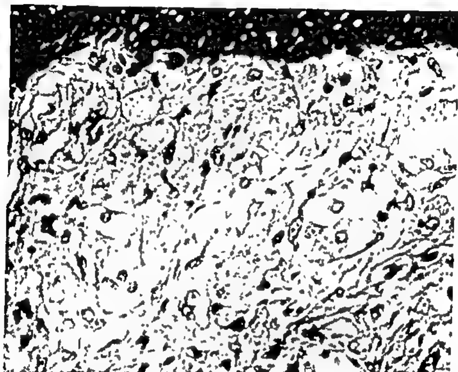


FIG 240. Granular-cell myoblastoma. The tumor is composed of large cells having a pale cytoplasm filled with coarse granules. (×400)

tender nodule, from 0.5 to 2 cm. in diameter, which may lie within the thickness of the skin or may be pedunculated. In some instances, the surface of the tumor is hyperkeratotic Subcutaneous myoblastomas consist of a firm nodule which may or may not be attached to the overlying skin.

Histopathology. On histologic examination, the cells of the tumor appear large and polyhedral Most cells measure from 20 to 60 microns in diameter, but some are even larger. They have a pale cytoplasm filled with coarse acidophilic granules (Fig. 240). The nuclei are small, round or oval and somewhat vesicular (Cipollaro and Einhorn). Some cells contain more than one nucleus. *Delicate strands* of collagen surround the cells of the tumor.

The overlying epidermis usually is hyperplastic and, not infre-



F o 21? Osteoma cut s Lo v magn ficat on The bone appears lamel lated about several Ha ers an canals (×100)



I 13 Osteoma cutis H gh magn ficat on of F gure 21? Th e bone l ned n many areas by osteoblasts In the *center of the field* several os eoclasts l e w th n a n che called Howsh p s lacuna (×?00)

The reasons these authors have given are first, granular cells occasionally are arranged *concentrically around a core consisting* of bundles of axis cylinders (Fust and Custer), second groups of granular cells have been *found within nerve* sheaths both within and in the vicinity of the tumor (Fust and Custer, Ashburn and Rodger) and, third, the granules stain slightly positive for lipids, suggesting that they form as a result of the disintegration of axis cylinders and myelin sheaths (Bangle)

In the rare cases of malignant granular cell myoblastomas, one can observe all stages of transition from typical granular cells to malignant spindle and giant cells devoid of granules Widespread hematogenous metastases may occur (Ross, Miller and Foote)

Differential Diagnosis. On cursory examination, the large, pale cells of the tumor resemble the foam cells of xanthoma However, the cells of granular cell myoblastoma contain a granular and not a foamy cytoplasm and take fat stains only very faintly Furthermore, in granular cell myoblastoma, the overlying epidermis tends to be hyperplastic rather than atrophic as in xanthoma

7. TUMORS OF OSSEOUS TISSUE

OSTEOMA CUTIS

Cutaneous bone formation may be primary (heterotopic) or secondary (metaplastic) Only lesions with primary bone *formation* should be called osteomas

In primary bone formation bone develops in areas which were not the site of previous lesions The bone probably develops from embryonal rests *Such* lesions therefore represent nevoid tumors or hamartomas (Hopkins, Dietrich Vero, Machacek and Bartlett)

In secondary bone formation, bone develops in areas of tissue degeneration *Bone may* develop in tumors particularly in the calcifying epithelioma of Malherbe (see page 368), in scar tissue (Lifga and Burns) in lesions of scleroderma in various granulomas and in areas of fat necrosis or hemorrhage Also *multiple small* foci of ossification may occur in the skin of the face in prolonged, severe acne with scarring (Leider) In all these instances the bone develops by metaplasia and frequently, though not always *calcification* precedes the ossification

Osteomas may be single (Dietrich) or multiple (Hopkins, Vero Machacek and Bartlett, Tijdens and Ruiter) Their clinical appearance is *not uniform* Usually they occur as small hard plaques or nodules within the dermis or subcutis

Keloid

Garb J and Stone M J Keloids Am J Surg 58 315 1942

Fibrosarcoma

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Foot N C Pathology in Surgery p 60 Philadelphia Lippincott 1945

Gentele H Malignant fibroblastic tumors of the skin Acta dermat.venereol 31 suppl 27 1951 (Good review)

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Foot N C Pathology in Surgery p 77 Philadelphia Lippincott 1945

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Savatard L Periarticular fibroma of the skin ("synovial lesions of the skin) Arch Dermat & Syph 9 441 1924

Woodburne A R Myxomatous degeneration cysts of skin and subcutaneous tissues Arch Dermat & Syph 56 407 1947

Lipoma Hibernoma and Liposarcoma

Brines O A and Johnson M H Hibernoma a special fatty tumor Am J Path 25 467 1949

Sternberg S S Liposarcoma arising within a subcutaneous lipoma Cancer 5 975 1952

Stout A P Liposarcoma—the malignant tumor of lipoblasts Ann Surg 119 86 1944

Sutherland J C Callahan W P and Campbell G L Hibernoma a tumor of brown fat Cancer 5 364 1952

Tedeschi C G Systemic multicentric lipoblastosis Arch Path 42 320 1946.

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Charache H Multiple neurofibroma with sarcomatous transformation and skeletal involvement Arch Dermat & Syph 40 18, 1939

Foot N C Histology of tumors of the peripheral nerves Arch Path 30 772 1940

Crill J and Kurma J F Recklinghausen's disease with unusual symptoms

How

Histopathology On histologic examination, one or several pieces of bone are observed within a lesion The bone appears lamellated in concentric rings about several Haversian canals These canals contain blood vessels and connective tissue (Fig 212) Most of the bone lamellae contain numerous small lacunae each filled with a cell These cells called osteocytes possess various shapes some of them are stellate Along the margin of the bone one sees many osteoblasts which build bone and a few osteoclasts which absorb bone The osteoblasts have small oval or elongated nuclei As they lay down bone substance they become enclosed in the bone as osteocytes The osteoclasts have multiple large nuclei and resemble multinucleated foreign body giant cells Frequently they lie within deep grooves called Howship s lacunae which extend into the bone substance (Fig 213)

The tissue surrounding the piece or pieces of bone often is highly vascular and cellular and may contain fat cells so that it resembles bone marrow

Occasionally one may find in osteomas not only bone but also fibrocartilage (Vero Machacek and Bartlett)

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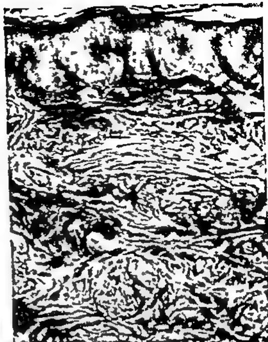
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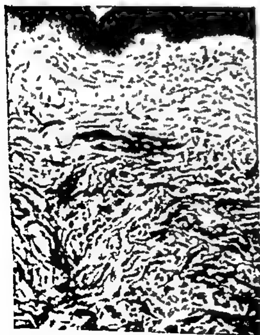
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PLATE 4



Leiomyoma Aniline blue (Mallory) stain This stain serves to differentiate collagen from smooth muscle With hematoxylin-eosin both stain red but with aniline blue collagen stains blue and muscle red (×175)



Blue nevus Numerous large, spindle shaped deeply pigmented cells are located in the lower dermis They are melanoblasts (×175)

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20

Pigmented Nevi and Malignant Melanoma

Pigmented nevi and malignant melanomas are composed of nevus cells Lentigo, the Mongolian spot and the blue nevus represent special types of pigmented nevi which will be discussed at the end of this chapter

PIGMENTED NEVUS

From a histologic point of view, it is practical to divide pigmented nevi into intradermal (resting) nevi and junction (active) nevi However, intermediary forms so called compound nevi, are common It is thus understandable that one cannot always predict from the clinical appearance whether a nevus is of the intradermal type or the junction type

The intradermal nevus, as a rule, is a circumscribed, smooth or slightly verrucous elevation which may or may not contain a number of hairs and varies in color from normal skin to dark brown Intradermal nevi are very rare on the palms, the soles and the genitalia Nevi located in these locations almost always are junction nevi

The junction nevus is a relatively flat or slightly raised, smooth, pigmented mark that is devoid of hairs Its color is light brown or brownish black rarely slate blue or bluish black The majority of the marks that are slate blue or bluish black are not junction nevi but blue nevi

Histogenesis of the Nevus Cell In former years the nevus cell had been thought to be of epidermal origin Unna believed that nevus cells were modified basal cells that had migrated (dropped off) from the epidermis into the dermis (Abtropfung theory) Today there are but few adherents of this theory (Allen) The great majority of investigators have accepted the theory first proposed by Masson in 1926, that both the melanocytes in the epidermis the so called clear cells, and the nevus cells are of neural origin (see page 5) Masson stated that nevus cells may develop from two sources from melanocytes in the epidermis and from schwannian cells of cutaneous nerves He believed that junction nevi develop exclusively from

melanocytes whereas compound and intradermal nevi develop from both melanocytes and schwannian cells So long as there was migration of melanocytes from the epidermis into the dermis the nevus was a compound nevus but when this migration ceased it became an intradermal nevus Thus compound and intradermal nevi according to Masson have a dual origin from two primordia which fused together This dualistic view of the origin of compound and intra

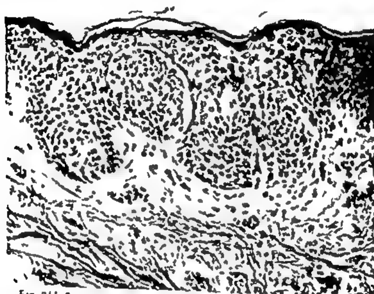


FIG 244 Junction nevus Well circumscribed nevus cell nests are present in the lower epidermis Otherwise the epidermis appears normal This type of junction nevus is not apt to become malignant (×200)

dermal nevi has been questioned by some authors (Lund and Stobbe) who believe that all pigmented nevi develop solely by dropping off of melanocytes

As evidence in favor of his theory of the ne ral or gin f

trands of schwan
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...) Additional evidence in favor of Masson s theory is the observation by Berkheiser and Rappoport that nevus cells may be found proliferating within the perineural sheath of superficial cutaneous nerves

20

Pigmented Nevi and Malignant Melanoma

Pigmented nevi and malignant melanomas are composed of nevus cells. Lentigo, the Mongolian spot, and the blue nevus represent special types of pigmented nevi which will be discussed at the end of this chapter.

PIGMENTED NEVUS

From a histologic point of view, it is practical to divide pigmented nevi into intradermal (resting) nevi and junction (active) nevi. However, intermediary forms, so-called compound nevi, are common. It is thus understandable that one cannot always predict from the clinical appearance whether a nevus is of the intradermal type or the junction type.

The intradermal nevus, as a rule, is a circumscribed, smooth or slightly verrucous elevation which may or may not contain a number of hairs and varies in color from normal skin to dark brown. Intradermal nevi are very rare on the palms, the soles and the genitalia. Nevi located in these locations almost always are junction nevi.

The junction nevus is a relatively flat or slightly raised, smooth pigmented mark that is devoid of hairs. Its color is light brown or brownish black, rarely slate blue or bluish black. The majority of the marks that are slate blue or bluish black are not junction nevi but blue nevi.

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outlined homogeneous cytoplasm The nucleus is large, … show varia … the epi … ey may

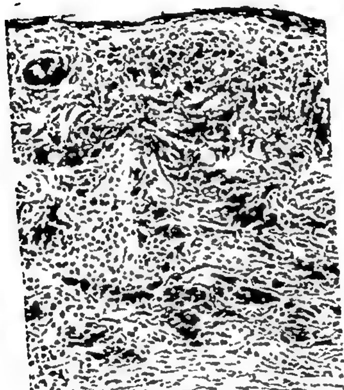


Fig 216 Junction nevus of the premalignant type Nevus cells lie diffusely scattered in the lower epidermis, which appears disorganized No actual invasion of the nevus cells into the dermis is present however The upper dermis contains a bandlike inflammatory infiltrate intermingled with melanophores (*It is possible that this type of junction nevus actually represents the earliest phase of a malignant melanoma*) (×200)

Junction Nevus This form of pigmented nevus, well described by Ebert by Traub and Keil and by Allen and Spitz, is characterized by the active formation of nevus cells in the lower epidermis—i e at the epidermal-dermal junction There are two types of junction nevi between which, however, there are transitions In one type, the newly formed nevus cells are present largely as well-circumscribed

Histopathology. In a junction (active) nevus, there is active formation of nevus cells in the basal layer of the epidermis (i e, at the epidermal dermal junction) and no nevus cell nests are found in the dermis In a compound nevus, there also is *junction activity*, but, in addition, well formed nevus cell nests are present in the dermis In an *intradermal nevus junction*, activity is no longer present and the

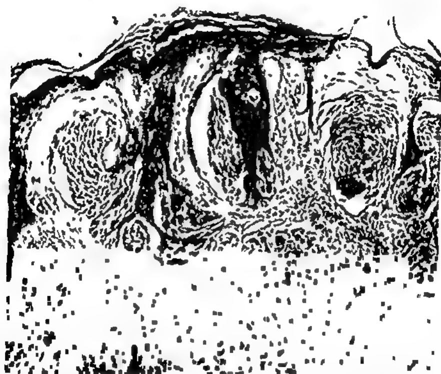


FIG 245 Nevus pigmentosus compound type The cells composing the intra epidermal and the subepidermal nevus cell nests are spindle shaped and resemble schwannian cells The nevus cell nests suggest Meissner tactile bodies (×100)

nevus cells are all located in the dermis However, completely intra dermal (resting) nevi are rare if serial sections are made it will be seen that nearly all intradermal nevi show at least a few areas of junction activity

That the development from junction nevus into a compound nevus and, further, into an intradermal nevus is a matter of aging of a nevus is suggested by the observation of Lund and Stobbe that a much higher percentage of nevi show junctional activity in children than in adults Only nevi located at the distal portions of the extremities were found consistently to be junction nevi, even in adults

The typical nevus cell is oval or cuboidal in shape

suggest Meissner tactile bodies (Fig 245) Although all junction nevi have a certain potentiality to become malignant, because they are active nevi, the danger of malignant degeneration is slight in this type of junction nevus with its regularly formed nests of nevus cells.



Fig [illegible] Nevus pigmentosus, intradermal type In the upper dermis the nevus cells lie in nests and cords In the lower dermis the nevus cells are arranged more loosely and embedded in fibrous tissue (×100)

In the second type of junction nevus, the premalignant junction nevus of Allen and Spitz, in which the nevus cells lie diffusely scattered in the lower epidermis, the lower epidermis appears disorganized by the presence of numerous vacuolated nevus cells with irregularly shaped nuclei (Fig 246) The nevus cells usually contain a considerable amount of melanin The border between the epidermis and the dermis is somewhat irregular, but no actual invasion of

nevus cell nests within the lower epidermis while in the other type the nevus cells are scattered diffusely through the lower epidermis This latter type of junction nevus has been called premalignant junction nevus by Allen and Spitz

In junction nevi with well circumscribed nevus cell nests in the lower epidermis the residual epidermis appears essentially normal

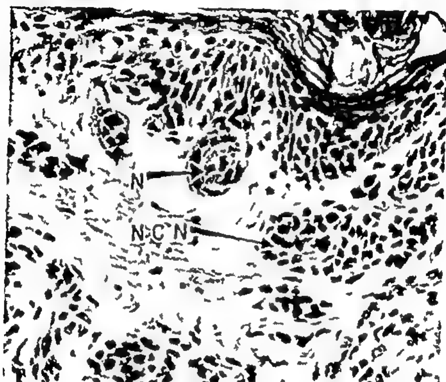


Fig 247 Nevus pigmentosus compound type In the basal layer one sees clear cells (melanocytes) lying singly and in nests Those lying in nests have already the appearance of nevus cells One nest (N) is in the stage of dropping off In addition typical nevus cell nests (N C N) lie free in the dermis Considerable amounts of melanin are present in the clear cells and in some of the nevus cell nests (×200)

(Fig 244) Frequently there are nests which lie beneath the epidermis but still are in contact with it and thus are in the stage of dropping off Occasionally in other parts of the same nevus one observes nevus cell nests located free in the dermis representing a development into a compound nevus The nevus cells contain varying amounts of melanin Melanophores may be present in the dermis but no inflammatory infiltrate is present The nevus cells comprising the intra epidermal nests have a regular cuboidal appearance In rare instances however they are spindle shaped and endowed with stroma so that they resemble schwannian cells and the cell nests

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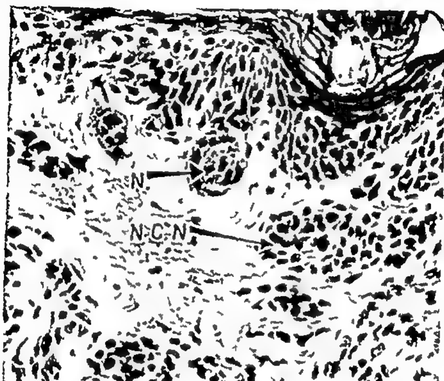


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fore can be taken as evidence of the benign nature of the nevus in which they occur They should not be confused with the giant cells occurring in so-called juvenile melanoma and occasionally, in malignant melanoma (see page 462) The nevus cells in the upper portion of the dermis frequently though not always contain melanin In the presence of much melanin melanophores are often present



FIG 250 Verrucous nevus pigmentosus There is lacelike downward growth of the epidermis around nests of nevus cells There are numerous multinucleated nevus cells (This is not a sign of *malignancy*) (×100)

No inflammatory reaction is present except in the case of mechanical irritation or of secondary infection In that case the inflammatory infiltrate however is focal rather than bandlike or diffuse as it is in malignant melanoma

In the lower dermis the nevus cells lie farther apart tend to be spindle shaped and are embedded in fibrous tissue The fibrous tissue may have the same loose wavy pale appearance as in neurofibroma (Cohen) Within this fibrous tissue the nevus cells may be arranged in narrow columns so that they suggest neural sheaths (neuroid tubes of Masson) In other areas the fibrous tissue may be in concentric arrangement (lames foliacées of Masson) resulting in structures resembling Meissner tactile bodies (Fig 249) Montgomery and

nevus cells in the dermis is present. The upper dermis contains numerous melanophores and, in many instances, also a bandlike inflammatory infiltrate. This type of junction nevus is often difficult to differentiate from an early malignant melanoma (see page 459) and it is possible that it actually represents the earliest phase of a malignant melanoma. In any event, it possesses a definite potentiality to progress into a malignant melanoma.

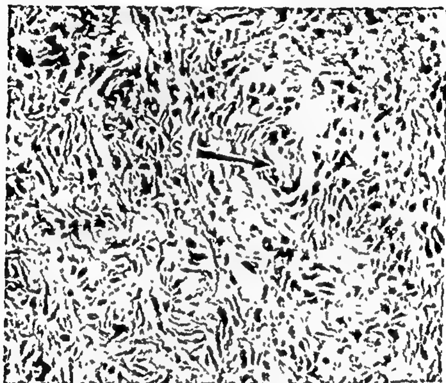


FIG 249 Nevus pigmentosus, intradermal type The lower dermis is shown The nevus cells are largely spindle shaped They are embedded in fibrous tissue which has the same loose, wavy, pale appearance as in neurofibroma In the center one sees a neuroid structure (N S) resembling a Meissner tactile body (×200)

COMPOUND NEVUS In a compound nevus one observes features of both junction nevus and intradermal nevus Nevus cell nests are seen within the epidermis, dropping off from the epidermis, as well as in the dermis free from contact with the epidermis (Fig 247).

INTRADERMAL NEVUS Intradermal nevi show, in the upper dermis, nests and cords of nevus cells surrounded by bundles of collagen (Fig. 248). In some instances the nevus cells lie in dense masses Not infrequently, one encounters multinucleated nevus cells showing either clumping or rosette like arrangement of small, darkly staining nuclei. These giant cells occur only in well matured nevi and, there-

melanomas whereas intradermal nevi, which show little or no junction activity, give rise to a malignant melanoma very rarely Especially the so-called premalignant junction nevus which is characterized by a diffu

out ter

upper



FIG 251 Margin of an early malignant melanoma On the left the epidermis is normal In the center because of the presence of many

... infiltrate extends on the left beyond the margin of the tumor under the normal epidermis. (×100)

In an

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dermis ... presence of numerous atypical nevus cells, appears vacuolated, torn apart and even disintegrated (Fig 251) This type of early malignant melanoma greatly resembles the premalignant type of junction nevus and differs from it only by the greater atypicality of the cells and the beginning invasion into the dermis (see also "Differential Diagnosis") As in the premalignant

Kernohan found such structures in 11 per cent of their material of pigmented nevi *With special nerve stains such as the Bodian stain* one frequently can see nerve fibers in the fibrous tissue They may occasionally be seen in close relation to the hair follicles

An occasional intradermal nevus is devoid of nevus cell nests in the upper dermis and shows only spindle shaped nevus cells embedded in abundant fibrous tissue Differentiation from a neurofibroma may then be difficult on a histologic basis (Cohen Becker) Such nevi are referred to as neural nevi

The epidermis over intradermal nevi may be normal but often is flattened because of pressure from below In some nevi the epidermis shows hyperkeratosis papillomatosis and lacelike downward growth (verrucous nevus pigmentosus) (Fig 250) In others large hair follicles *are present (nevus pigmentosus et pilosus)*

MALIGNANT MELANOMA

Malignant melanoma may arise as such or may develop from a pigmented nevus If a malignant melanoma arises from a pigmented nevus such nevus is almost invariably of the junction type Clinical evidence that a malignant change is occurring in a pigmented nevus is presented by an increase in the size of the lesion an increase in the depth of pigmentation and not infrequently the development of an inflammatory border with or without spilling of pigment from the lesion into the surrounding skin

Early malignant melanoma is characterized by a gradually enlarging *deeply pigmented nodule usually surrounded by erythema* Later the lesion becomes fungating and satellite lesions may appear Ulceration is a late symptom In occasional instances hyperpigmentation is slight or absent

Metastasis takes place at first through the lymphatics resulting in *involvement of the regional lymph nodes Blood spread is a late event* and may be absent until nearly the end When it occurs metastases are usually widespread The liver the lungs the brain and the skin are the most common sites of hematogenous metastases

Malignant melanoma is rare before puberty and when it occurs it is usually clinically benign For instance in a series of 13 *histologically* malignant melanomas in children published by Spitz only one *death occurred*

Histopathology The malignant changes invariably begin at the dermal epidermal junction irrespective of whether a malignant melanoma starts as such or develops from a pigmented nevus (Miescher) For this reason pigmented nevi with considerable junction activity like the junction nevus *predispose* to the development of malignant

melanomas, whereas intradermal nevi, which show little or no junction activity, give rise to a malignant melanoma very rarely Especially ... ed by ... with ... in the

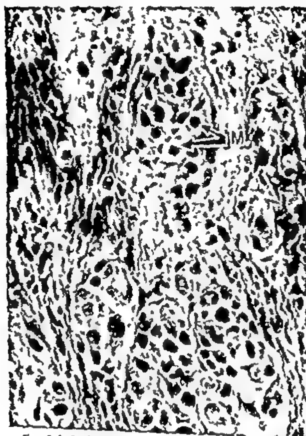


Fig 251 Margin of an early malignant melanoma. On the left, the epidermis is normal In the center, because of the presence of many ...

left beyond the margin of the tumor under the normal epidermis (×100)

In an early malignant melanoma and at the advancing border of older lesions one may find considerable changes within the epidermis but only slight invasion of the dermis by tumor cells The lower epidermis, because of the presence of numerous atypical nevus cells, appears vacuolated, torn apart and even disintegrated (Fig 251) This type of early malignant melanoma greatly resembles the premalignant type of junction nevus and differs from it only by the greater atypicality of the cells and the beginning invasion into the dermis (see also "Differential Diagnosis") As in the premalignant

irregularly shaped, often deeply pigmented nests of atypical nevus cells which may show mitotic figures (Fig 253) The upper epidermis may be invaded and become so permeated with tumor cells that it



[illegible] (X400)

disintegrates and ulceration results (Fig 254) In addition, there is deep penetration of the *dermis* by atypical nevus cells Simultaneously with the downward *penetration of the* nevus cells, the epidermis [illegible] ion of the rete [illegible] by the down[illegible]

The size and the shape of the tumor cells *in the* dermis show great

type of junction nevus, one finds in the upper dermis, close to the epidermis, a dense, bandlike inflammatory infiltrate intermingled with many melanophores This inflammatory infiltrate often extends for a distance away from the malignant melanoma under the normal



FIG 252 Malignant melanoma Low magnification There is considerable junction activity One finds not only dropping off of nevus cells and nevus cell nests downward into the dermis but also migration upward into the stratum malpighii The tumor cells are largely of the cuboidal type and lie in alveolar formations (×100)

epidermis (Fig 251) It is of interest that once deep invasion of the dern [illegible] cells has taken place, the inflam mato [illegible] and in well progressed malignant melano[illegible] absent except at the margins if there is extension of the tumor

In an advanced malignant melanoma there is also considerable irregular junction activity (Fig 252) The epidermis contains large,

in malignant melanoma usually is strongly positive in the cells near the dermo-epidermal junction The tumor cells deep in the dermis, however react weakly or not at all (Miescher)

In children malignant melanoma is uncommon and even lesions which histologically have the appearance of malignant melanoma

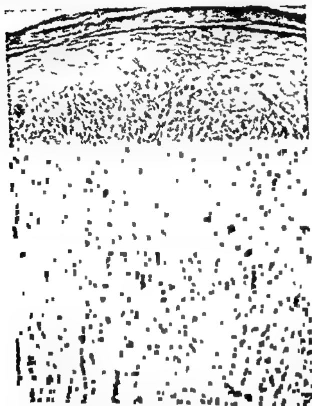


Fig. 255 Malignant melanoma The tumor cells are fusiform and lie in irregular strands The tumor thus resembles a ... ence of ... melanin ... melanophores (×100)

cause metastases only in the rarest instances These malignant melanomas generally referred to as juvenile melanomas differ ... histologic ...
In about c...
giant cells ... do not occur in adult malignant melanoma (Spitz, Haber) These giant cells have a round, oval or stellate

variation Nevertheless two types of cells can be recognized clearly a cuboidal and a fusiform type Although most tumors show both cell types almost invariably one type greatly predominates Predominance of cuboidal cells is much more common than predominance of fusiform cells The cuboidal cells tend to lie in alveolar formations (Figs 252 and 253) The fusiform cells tend to lie in irregular branching strands (Fig 255) Tumors in which fusiform cells predominate

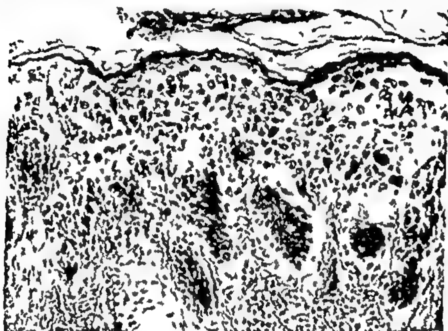


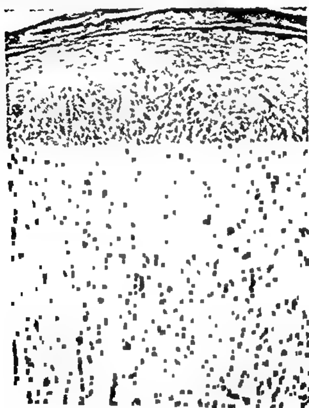
Fig 254 Malignant melanoma The epidermis has disintegrated due to permeation with tumor cells (×200)

resemble fibrosarcoma but differ from it by the presence of junction activity Mitotic figures are usually present in malignant melanoma but often only in small numbers They should be searched for because their presence is of great value as evidence that the tumor is malignant inasmuch as in pigmented nevi mitotic figures are very rare or absent (Miescher) Bizarre multinucleated giant cells occur occasionally

The amount of melanin varies considerably in malignant melanomas In some tumors considerable amounts of melanin are present in both tumor cells and melanophores In others particularly in rapidly growing tumors there may be no evidence of melanin in hematoxylin eosin stains Such tumors have been referred to as amelanotic malignant melanoma However staining of sections with silver will reveal in most instances a few cells containing melanin Irrespective of the amount of melanin present the dopa reaction

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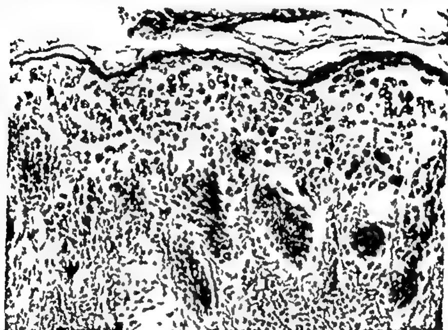


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a u Fecker Gawley and Curtis) The basal layer of the projecting rete ridges shows considerable hyperpigmentation and a great increase in the number of clear cells No junction activity i e dropping-off of clear cells is observed The upper dermis often contains melano



Fig 256 Lentigo The rete ridges are elongated Numerous clear cells (melanocytes) are present in the basal layer (X200)

phores and sometimes a mild perivascular lymphocytic infiltrate In the case of senile lentigo the upper dermis also shows basophilic degeneration of the collagen

Whether or not lentigo can progress by the onset of dropping-off activity into a junction nevus is not yet fully decided but this appears likely since junction nevi not infrequently show at the per

(fr ... pigmentation of the basal layer but no elongation of the rete ridges

MONGOLIAN SPOT

The typical Mongolian spot occurs as a bluish gray discoloration in the lumbosacral region. It is found with great regularity in mem

shape and an acidophilic cytoplasm with one or more large, vacuolated, irregularly outlined nuclei. They differ from the giant cells of intradermal nevi, which have small, deeply basophilic nuclei, and from those found occasionally in malignant melanoma, which are larger and more bizarre.

The histologic appearance of metastatic lesions of the skin differs from that of primary lesions by the absence of junction activity. Metastatic lesions never show any inflammatory infiltrate (Dixon).

Differential Diagnosis. Differentiation of early malignant melanoma from junction nevus may cause considerable difficulties. That is easily explainable: a junction nevus may develop into a malignant melanoma. If this development proceeds slowly, as it often does, tumors in an intermediate stage of development result. The type of junction nevus most likely to undergo malignant degeneration is the one with diffusely scattered nevus cells in the lower epidermis, the so called premalignant junction nevus (page 455, Fig. 246). This type of junction nevus, like early malignant melanoma, has numerous vacuolated nevus cells with atypical nuclei in the lower epidermis which thus appears disorganized. It may show, in addition, a bandlike inflammatory infiltrate in the upper dermis. It differs from malignant melanoma by the absence of invasion of the nevus cells into the dermis and by the absence of mitotic figures. However, these are not absolutely reliable criteria, and in some instances a decision as to whether malignancy exists already is impossible. There are some authors, like Miescher, who are inclined to regard as malignant any junction nevus showing a bandlike inflammatory infiltrate. According to Miescher, this is evidence that aggressive invasion is being fought off. It matters little, however, whether such junction nevi are called "premalignant" or "early malignant"; it is important that they require wide excision.

A highly malignant amelanotic melanoma may be difficult to differentiate from a highly malignant fibrosarcoma or a Grade IV spindle cell squamous cell carcinoma. For their differentiation see under Fibrosarcoma, page 110.

LENTIGO

Lentigo is a smooth, not infiltrated, dark brown mark usually measuring only a few millimeters in diameter. A juvenile and a senile type occur. Juvenile lentigines begin to appear in childhood and occur on all parts of the body. Senile lentigines ("liver spots") occur in old age on the dorsa of the hands, on the forearms and on the face. Both types are benign. Clinical differentiation from junction nevus may be impossible.

Histopathology The histologic findings are the same in juvenile and senile lentigo The rete ridges appear elongated and club shaped (Fig 256) Eccentric thumb like buds may project from them (Zeisler and Becker Cawley and Curtis) The basal layer of the projecting rete ridges shows considerable hyperpigmentation and a great increase in the number of clear cells No junction activity, i e dropping-off of clear cells is observed The upper dermis often contains melanophores and sometimes a mild perivascular lymphocytic infiltrate In the case of senile lentigo the upper dermis also shows basophilic degeneration of the collagen



Fig 256 Lentigo The rete ridges are elongated Numerous clear cells (melanocytes) are present in the basal layer (×200)

Whether or not lentigo can progress by the onset of dropping-off activity into a junction nevus is not yet fully decided but this appears likely since junction nevi not infrequently show at their periphery the histologic picture of lentigo

Differential Diagnosis Lentigo must be differentiated from ephelis (freckle) Ephelides show hyperpigmentation of the basal layer but no elongation of the rete ridges

MONGOLIAN SPOT

The typical Mongolian spot occurs as a bluish gray discoloration in the lumbosacral region. It is found with great regularity in mem

bers of the Mongolian race but occurs occasionally also in other races It is present at birth and gradually fades

Occasionally, Mongolian spots occur outside the usual location as aberrant Mongolian spots (Cole, Hubler and Lund) They may even be multiple (Carleton and Biggs) or appear during adult life and gradually increase in size (Pariser and Beerman)

Histopathology. The dermis shows, especially in its midportion fusiform and stellate cells filled with brown pigment granules These cells lie widely scattered as well as in small groups They give a positive dopa reaction (see page 12), indicating that they are melanocytes (Cole, Hubler and Lund)

Formerly, the cells composing the Mongolian spot were regarded as mesodermal melanocytes, as opposed to the epidermal melanocytes forming pigmented nevi However, the theory of the neural origin of melanocytes has done away with this artificial division into epidermal and mesodermal melanocytes The cells of the Mongolian spot (as well as those of the blue nevus—see below) are now regarded as melanocytes which in their embryonal migration from the neural crest to the epidermis failed to reach the epidermis but became arrested in the dermis (Montgomery)

BLUE NEVUS

The blue nevus is a sharply circumscribed, round or oval, soft nodule of slate blue or bluish black color which measures, as a rule, only a few millimeters in diameter There usually is only one lesion, although multiple blue nevi do occur In rare instances, large, infiltrated plaques have been encountered (Upshaw, Ghormley and Montgomery) Malignant degeneration of blue nevi is very rare, but it does occur (Montgomery and Kahler Allen and Spitz) Metastases may develop and cause death

Histopathology The cells composing blue nevi are of the same type as those composing the Mongolian spot They are dopa positive melanocytes which became arrested in the dermis during their embryonal migration from the neural crest to the epidermis (Montgomery) The number of these cells is however much greater in blue nevi than in the Mongolian spot

In the blue nevus greatly elongated melanocytes lie grouped in irregular masses and bundles in the middle and the lower thirds of the dermis (Fig 257) Occasionally these cell masses extend into the subcutaneous layer or close to the epidermis The epidermis, however, is normal The melanocytes are spindle shaped and have long bipolar, occasionally branching processes (see Plate 4) They lie predominantly with their long axis parallel to the epidermis Most of

them are filled with numerous fine granules of melanin, often so completely that their nucleus cannot be visualized. In addition, melanophores (chromatophores) frequently occur within and beside the masses of melanocytes. The melanophores differ from the melanocytes by being shorter and thicker and by containing coarser granules (Fig. 258). In addition, the melanocytes are dopa positive while the melanophores are dopa negative.



FIG. 257. Blue nevus. Low magnification. Numerous spindle-shaped melanocytes, filled with melanin, lie grouped in irregular bundles in the middle and the lower thirds of the dermis and in the subcutaneous fat. (×50)

Blue nevi may undergo fibrosis. In that case, thick bundles of collagen separate the melanocytes. In occasional instances, the presence of a pigmented nevus *and of a blue nevus in the same lesion* has been reported (Montgomery and Kahler).

The blue color which the blue nevus presents ... from ...

... and large, irregularly hyperchromatic nuclei), blue nevi in which *malignant* degeneration has oc

be ... asionally also in other races It ... utside the usual location as aberrant Mongolian spots (Cole, Hubler and Lund) They may even be multiple (Carleton and Biggs) or appear during adult life and gradually increase in size (Pariser and Beerman)

Histopathology. The dermis shows, especially in its midportion fusiform and stellate cells filled with brown pigment granules These cells lie widely scattered as well as in small groups They give a positive dopa reaction (see page 12), indicating that they are melanocytes (Cole, Hubler and Lund)

Formerly, the cells composing the Mongolian spot were regarded as mesodermal melanocytes, as opposed to the epidermal melanocytes forming pigmented nevi However, the theory of the neural origin of melanocytes has done away with this artificial division into epidermal and mesodermal melanocytes The cells of the Mongolian spot (as well as those of the blue nevus—see below) are now regarded as melanocytes which in their embryonal migration from the neural crest to the epidermis failed to reach the epidermis but became arrested in the dermis (Montgomery)

BLUE NEVUS

The blue nevus is a sharply circumscribed, round or oval, soft nodule of slate blue or bluish black color which measures, as a rule, only a few millimeters in diameter There usually is only one lesion, although multiple blue nevi do occur In rare instances, large, infiltrated plaques have been encountered (Upshaw, Ghormley and Montgomery) Malignant degeneration of blue nevi is very rare, but it does occur (Montgomery and Kahler, Allen and Spitz) Metastases may develop and cause death

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FIG 257 Blue nevus Low magnification Numerous spindle shaped *melanocytes* filled with melanin lie grouped *in irregular* bundles in the middle and the lower thirds *of the dermis* and *in the* subcutaneous fat (×50)

Blue nevi may undergo fibrosis. *In that case* thick bundles of col lagen separate the melanocytes *In occasional* instances the presence of a pigmented nevus and of a blue nevus in the same lesion has been reported (Montgomery and Kahler)

The blue color which the blue nevus presents clinically results from the deep location of the *pigment* ...

... large irregularly hyperchro matic nuclei) blue nevi in which malignant degeneration has oc

curred show areas of necrosis as a diagnostically important feature (Allen) The malignant cells may appear swollen and vacuolated and may lose their spindled character so that recognition of the lesion as

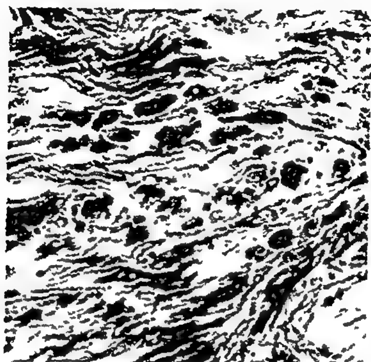


FIG 258 Blue nevus High magnification of Figure 257 There are numerous spindle shaped melanocytes filled with fine melanin granules In addition melanophores filled with large irregularly shaped melanin granules are present in the middle third of the field shown (×400)

a malignant blue nevus must be based on the presence of residual portions of the original benign blue nevus

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21

Lymphoma and Myelosis

Lymphoma designates a group of malignant tumors arising, usually in multiple foci, from the lymphoid reticular system. Myelosis is a designation for malignant tumors arising, invariably in multiple foci, from the myeloid system.

LYMPHOMA

Lymphomas are composed primarily of immature and mature cells of the lymphoid reticular system. The mother cell of the lymphoid reticular system is the lymphoid reticular stem cell. This cell may differentiate into a lymphoid cell (lymphoblast to lymphocyte) or into a reticular cell (reticulum cell to histiocyte to fibroblast) (see Chart 2, page 33). The type of lymphoma which results in a given case depends on the degree of immaturity of the cells and on the direction of their differentiation.

The lymphomas may start as a solitary lesion and may remain as such for a long period of time. As a rule, however, the lesions are multiple from the beginning. The multiplicity of the lesions is due to the systemic nature of the disease and usually not to metastasis. Occasionally, however, dissemination by metastasis occurs in addition.

Leukemia is frequent with some types, rare with other types of lymphoma. Leukemia is merely the result of a release of immature tumor cells into the blood stream and does not represent a separate form of disease. Invariably one finds in patients with leukemia involvement of the bone marrow. However, marrow involvement may occasionally be found in patients with normal blood pictures (Gall and Mallory).

Just as leukemia is a part of the disease which may be present or absent, so involvement of the skin is a variable manifestation of lymphoma, found more frequently in some forms of lymphoma than in others, but a possible occurrence in all. In a review of 618 cases of lymphoma, Gall and Mallory found leukemic blood changes in 17 per [illegible] 90 per cent [illegible] main groups, the monomorphous and the polymorphous group [illegible] n the

former the tumors are composed entirely of lymphoid reticular cells while in the latter group the tumors show an admixture of inflammatory cells The following classification which is based on that by Gall and Mallory is suggested

Monomorphous group
1 Stem cell lymphoma
2 Reticulum cell lymphoma
3 Lymphoblastic lymphoma
4 Lymphocytic lymphoma
5 Follicular lymphoma (Brill Symmers)
Polymorphous group
6 Hodgkin s disease
7 Mycosis fungoides

It is impossible to assign every case of lymphoma to one of these seven types because some tumors are in an intermediary stage of differentiation or show features of more than one type Furthermore different types of lymphoma may be encountered in different areas of the same patient and not infrequently as the disease progresses the lesions may become less differentiated and require reassignment to another type (Keim Gall and Mallory Herbut Miller and Erf)

The terms round-cell sarcoma lymphosarcoma and reticulum-cell sarcoma formerly were and occasionally still are used as designation for single tumors of lymphoma The use of the term sarcoma is misleading however because even in the case of a single lesion the potentially systemic nature of the disease may become apparent at any time If [illegible]

[illegible] specific and nonspecific lesions Nonspecific lesions which when found in association with leukemia are often referred to as leukemids may consist of macules papules purpuric lesions vesicles bullae eczematous lesions and exfoliative dermatitis Specific lesions may consist of plaques nodules and tumors, in addition however any of the lesions mentioned as occurring as a nonspecific reaction may show a specific lymphomatous infiltrate This holds true especially of eczematous lesions and exfoliative dermatitis Thus it is impossible to predict always *from the* clinical appearance whether a lesion is nonspecific or specific

Histopathology Histologically *specific lesions* of lymphoma of the skin show either large masses of lymphoma cells patchy accumulations of lymphoma cells *or an* inflammatory *infiltrate* intermixed with lymphoma cells The *lymphoma cells* vary with the type of lymphoma and may be immature lymphoid reticular cells such as

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[illegible]

groups: the monomorphous and the polymorphous [illegible]

forms of lymphoma They occur most commonly in stem-cell lymphoma reticulum-cell lymphoma, lymphoblastic lymphoma and in the tumor stages of Hodgkin's disease and mycosis fungoides The tumor masses may be sharply demarcated, but usually there are small, outlying islands of tumor cells and, in addition, single rows of lym

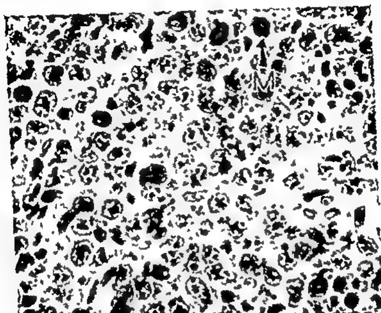


Fig 260 Stem-cell lymphoma High magnification of Figure 259 The tumor cells possess abundant, pale staining cytoplasm and large round nuclei The nuclei contain delicate dustlike chromatin and *one or several prominent nucleoli* Mitotic figures are numerous A large atypical *mitotic figure* (M) is present in the upper right corner (×400)

phoma cells which extend from the main tumor mass ...

... of the breast—see page 399 ...

ly...

th... may occur even in the subcutaneous tissue They usually show a blood vessel in their center around which the infiltrate lies as a thick *sleeve*

An inflammatory infiltrate intermixed with tumor cells is the usual picture in Hodgkin's granuloma and in the erythematous and the

stem cells, reticulum cells and lymphoblasts, or mature lymphoid reticular cells, such as histiocytes and lymphocytes Usually atypical cells and a varying number of mitotic figures are present Nonspecific lesions consist of an inflammatory infiltrate without immature cells

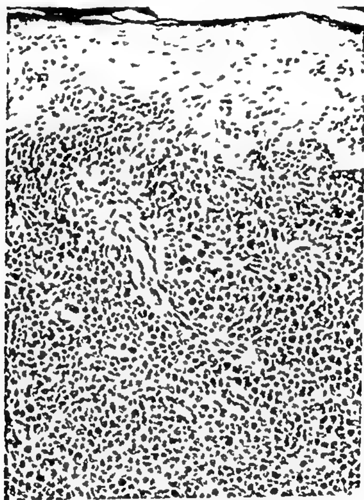


Fig 259 Stem cell lymphoma Low magnification A large mass of loosely packed tumor cells is present in the dermis (×100)

It is probable that most if not all nonspecific lesions result from lymphoma cells (Gates) It may be assumed that the lymphoma cells either have been overwhelmed and removed by the inflammatory infiltrate which they themselves have provoked or do not differ sufficiently in their appearance from the inflammatory cells to be recognized as lymphoma cells

Large masses of lymphoma cells in the dermis and the subcutaneous layer, which clinically appear as cutaneous tumors may occur in all

ture reticular cell (histiocyte) [The author prefers to call the immature reticular cell a reticulum cell, and the mature reticular cell a histiocyte However, it should be kept in mind that many authors use the term reticulum cell also for the mature reticular cell (see page 35)] The reticulum cells in reticulum-cell lymphoma have an eosinophilic cytoplasm the border of which tends to be irregular in

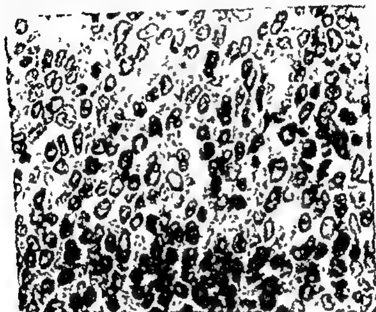


Fig 261 Reticulum-cell lymphoma The tumor cells possess abundant pale staining cytoplasm and variously shaped nuclei Some are round but most are oval or kidney shaped The nuclei are pale staining and possess a distinct nuclear membrane (×400)

outline suggesting ameboid propensities The nuclei differ in configuration a few are round more are oval and still others are kidney shaped They are pale staining and appear vesicular because of the presence of a well defined, strongly basophilic nuclear membrane (Fig 261) They show a moderately heavy chromatin network, nucleoli are rarely evident A moderate number of mitotic figures is present The reticulum cells, being immature, form only a scanty reticulum network In most tumors a fair number of mature reticular cells (histiocytes) are present Tumors containing many histiocytes may have a well-developed reticulum network Lymphocytes are sometimes also found presumably evidence of exudative reaction (Wayson and Weidman, Gall and Mallory, Director and Kern)

plaque stages of mycosis fungoides This type of infiltrate, too, tends to have a patchy arrangement

So called nonspecific lesions, which show a nonspecific chronic inflammatory infiltrate, occur in the skin, particularly in early mycosis fungoides, in Hodgkin's disease and in lymphocytic lymphoma

1 Stem Cell Lymphoma

Stem cell lymphoma produces, as a rule, tumorlike lesions In about one third of the cases, it arises as a single lesion, either in the skin or elsewhere, and may remain localized for some time Leukemia is very rare

Histopathology. The lesions are composed of large masses of cells (Fig 259) The vast majority of cells are stem cells, but most tumors show an admixture of reticulum cells Stem cells are large in size and possess abundant, pale staining cytoplasm They may lie separate from one another, but frequently the cytoplasm of neighboring cells is fused Their nuclei are large, from two to four times the size of a normal lymphocyte, round and filled with delicate, dustlike chromatin They usually possess one but occasionally several large, deeply staining nucleoli (Fig 260) Typical and atypical mitotic figures are numerous Stem cells are too immature to form reticulum fibers (Gall and Mallory)

2 Reticulum Cell Lymphoma

Tumorlike lesions are the most common type In about one third of the cases reticulum cell lymphoma like stem cell lymphoma starts as a solitary lesion Occasionally the first lesion or group of lesions occurs in the skin (Director and Kern)

If leukemia develops in reticulum cell lymphoma, it is of the monocytic variety, since the blood monocyte is derived from the reticular group of cells (Herbut and Miller) True monocytic leukemia is sometimes referred to as the Schilling type of monocytic leukemia, in contrast to the Naegeli type of monocytic leukemia in which monocyte like cells arise from myeloblasts and which therefore is a form of myeloid leukemia (Montgomery and Watkins) (see page 195) In the presence of monocytic leukemia the skin frequently shows purpuric vesicular and papular lesions (Herbut and Miller) In addition plaques and tumorlike lesions may be present (Wayson and Weidman) Exfoliative dermatitis may occur (Montgomery and Watkins) Swelling and ulceration of the gums are frequent

Histopathology. In tumorlike lesions, large compact masses of cells are present The type cell is an immature reticular cell (reticulum cell) This cell is smaller than a stem cell but larger than a ma

ture reticular cell (histiocyte) [The author prefers to call the im mature reticular cell a reticulum cell, and the mature reticular cell a histiocyte However, it should be kept in mind that many authors use the term reticulum cell also for the mature reticular cell (see page 35)] The reticulum cells in reticulum cell lymphoma have an eosinophilic cytoplasm the border of which tends to be irregular in

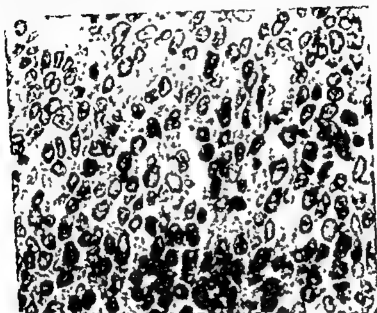


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In small cutaneous lesions, as they occur particularly in association with monocytic leukemia, the infiltrate is less extensive and the cells are of smaller size. Nevertheless, the cells have the same appearance as in the large lesions having indented or kidney shaped, pale nuclei with a distinct nuclear membrane (Hubler and Nether

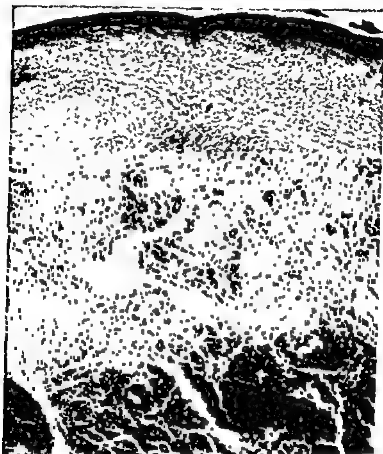


Fig 262 Lymphoblastic lymphoma. Low magnification. Masses of densely packed tumor cells are present in the lower dermis (×50)

ton). In the presence of monocytic leukemia, extravasation of erythrocytes is frequently found

Differential Diagnosis. It is important not to confuse reticulum-cell lymphoma with reticulo endotheliosis (histiocytosis) of the Letterer-Siwe and Hand Schuller Christian types (see page 262) Reticulum-cell lymphoma and reticulo endotheliosis are occasionally so difficult to *differentiate histologically that in the past they have* been confused (Sweitzer, Winer and Cumming) Reticulo endotheliosis, like reticulum cell lymphoma, *shows large, irregularly shaped* reticular cells (histiocytes) but shows no atypical reticular cells, par-

ticularly no mitotic figures. The lesions contain, as a rule, eosinophils and one may find cholesterol deposits in the reticular cells.

3. LYMPHOBLASTIC LYMPHOMA

The cutaneous lesions consist predominantly of nodules, plaques and tumors. Purpura is not uncommon.

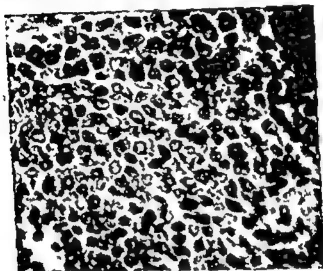


FIG. 263. Lymphoblastic lymphoma. High magnification of Figure 262. The cells have only little cytoplasm. The nuclei lie therefore more densely packed than in stem cell lymphoma or ... [illegible] ... phocytes. A few lymphocytes are present. (×400)

Leukemia develops in a large percentage of cases—according to Gall and Mallory, in 40 per cent. The type is lymphatic leukemia.

Histopathology. The cutaneous lesions show usually large masses of tumor cells and occasionally a patchy infiltrate. Lymphoblasts predominate, but in most lesions stem cells and lymphocytes are present in moderate number. Lymphoblasts possess a narrow basophilic rim of cytoplasm and large round or slightly indented nuclei. Because of the relatively small amount of cytoplasm, the nuclei lie close together, much closer than in stem-cell or reticulum-cell lymphoma (Fig. 262). The nuclei are larger than those of lymphocytes and more uniform in appearance than those of stem cells or reticulum cells. The chromatin in the nuclei of lymphoblasts is distributed rather evenly and much less clumped than in lymphocytes, giving the nuclei

a vesicular appearance (Fig 263) Nucleoli are observed infrequently Mitotic figures are usually numerous A fine, evenly distributed reticulum framework is occasionally present (Gall and Mallory)

4 Lymphocytic Lymphoma

Cutaneous nodules, plaques and tumors occur Exfoliative dermatitis is relatively common In addition, *nonspecific lesions*, especially

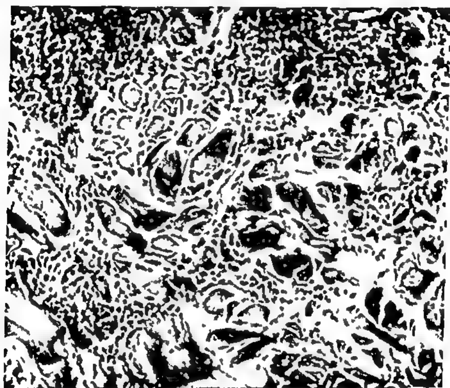


Fig 264 Lymphocytic lymphoma In the upper third of the photograph one sees the periphery of a large mass of tumor cells Rows of tumor cells extend from there between the collagen bundles The cells are indistinguishable from normal lymphocytes (×200)

papules and petechiae, may be observed Of interest is the occasional occurrence of generalized herpes zoster in association with lymphocytic lymphoma (see page 491)

Lymphatic leukemia occurs in about half the cases of lymphocytic lymphoma (Gall and Mallory)

Histopathology. The specific cutaneous lesions may show either large masses of cells (Fig 264), scattered patches of cells (Fig 265) or, in the case of exfoliative dermatitis, a diffuse infiltrate in the upper dermis

In lesions showing large masses or scattered patches of cells, the predominating cell is indistinguishable from a normal lymphocyte. Lymphoblasts may be present in small numbers Mitotic figures are sparse Thus, the infiltrate appears homogeneous At the periphery of the large masses one frequently sees rows of tumor cells extending between and even around intact collagen bundles in a similar way as it may be observed in scirrhous metastatic carcinoma



FIG 265 Lymphocytic lymphoma Sharply demarcated, large patches of lymphocytes are distributed through the dermis Most patches show a blood vessel in their center (×100)

If the infiltrate consists of scattered patches, some difficulty may arise in differentiating lymphocytic lymphoma from chronic discoid lupus erythematosus in which the infiltrate is also patchy In lymphocytic lymphoma however, the patches are distributed indiscriminately throughout the dermis without predilection to the upper dermis and the vicinity of the cutaneous appendages In addition the patches are uniformly composed of lymphocytes without an admixture of plasma cells and histiocytes as in lupus erythematosus Furthermore the epidermal changes associated with lupus erythematosus are absent

In instances of exfoliative dermatitis one finds a diffuse infiltrate in the upper dermis It is composed, in addition to lymphocytes, of

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6 Hodgkin's Disease

In most instances Hodgkin's disease affects primarily and predominantly the lymph nodes In rare instances the first lesions are noted in the skin (Reimann Havens and Herbut)

Cutaneous lesions are observed quite frequently Nonspecific lesions however are more common than specific lesions Most commonly found are papular lesions which are intensely pruritic Other lesions are eczematous patches generalized exfoliative dermatitis nodules or tumors The latter frequently undergo ulceration (Senear and Caro) Generalized herpes zoster occurs occasionally (see page 491)

Histopathology In the specific lesions of Hodgkin's disease two stages can be recognized Hodgkin's granuloma and Hodgkin's sarcoma Hodgkin's sarcoma may follow Hodgkin's granuloma but the disease may show the morphology of Hodgkin's sarcoma at the onset (Jackson and Parker)

Hodgkin's granuloma is composed of a polymorphous infiltrate The majority of the constituent cells are the usual components of a chronic inflammatory infiltrate namely eosinophils neutrophils lymphocytes plasma cells histiocytes and fibroblasts In addition [illegible]

from stem cells They occur as mononucleated and multinucleated cells The mononucleated Sternberg Reed giant cell possesses a very large irregularly shaped nucleus The multinucleated Sternberg Reed giant cell has either a double nucleus (mirror image nucleus) or several nuclei of dissimilar size and shape clustered in the center of the cell The nuclei of both mononucleated and multinucleated Sternberg Reed cells contain a prominent nucleolus and heavy clumps of chromatin Mitotic figures occur with moderate frequency in the stem cells reticulum cells and Sternberg Reed cells Hodgkin's granuloma has a tendency to focal necrosis and in lesions showing this phenomenon phagocytes are quite numerous Eosinophils are usually but not invariably present In some cases they constitute the predominant cell Collagen production is the result of the natural evolution of maturing histiocytes into fibroblasts Collagen production is scanty in the early phases and progresses steadily until broad fibrous septa separate the foci of cellularity into islands (Jackson and Parker)

Hodgkin's sarcoma differs from Hodgkin's granuloma by the preponderance of stem cells reticulum cells and Sternberg Reed cells

neutrophils, eosinophils and plasma cells, resulting in an inflammatory infiltrate of banal appearance However, immature lymphocytes and mitotic figures here and there usually reveal the nature of the process Sometimes one also finds in the lower cutis variously sized patches *composed solely of lymphocytes, further facilitating the* diagnosis (Keim).

5 Follicular Lymphoma (Brill-Symmers)

Follicular lymphoma, also called Brill Symmers disease, occurs predominantly *in the lymph nodes, causing considerable enlargement* of the affected lymph nodes The skin is involved in only rare instances, showing discrete, firm, brownish to reddish nodules (Gall Morrison and Scott)

Follicular lymphoma of the lymph nodes was described originally as a hyperplasia but is now generally regarded as lymphoma, because it may progress into other forms of lymphoma and is ultimately fatal

Histopathology. The enlarged lymph nodes show replacement of the normal architecture by numerous round, follicle like nodules of varying size These follicles are composed of densely packed lymphoblasts and are surrounded by a thin rim of normal small lymphocytes Mitotic figures are present within them in small number Very frequently, the follicles are partially separated from the surrounding stroma by fissures *Although these fissures are an artefact caused by* shrinkage of tissue during fixation they are of considerable aid in the diagnosis of follicular lymphoma (Gall, Morrison and Scott)

The cutaneous lesions, in rare instances, show the same follicular pattern as the lymph nodes Usually however, the infiltrate has the appearance of either lymphocytic or lymphoblastic lymphoma

Differential Diagnosis. Follicular lymphoma of the lymph nodes must be differentiated from reactive hyperplasia such as occurs in dermatopathic lymphadenitis (see page 75) It differs from the latter by the presence of mitotic figures, obliteration of the sinuses, absence *of inflammatory cells and absence of phagocytosis*

Confusion of follicular lymphoma with dermatopathic lymphadenitis has caused several authors to describe erroneously the occurrence of generalized exfoliative dermatitis in Brill Symmers disease (Combes and Bluefarb Rost) These cases actually were instances of idiopathic generalized exfoliative dermatitis with secondary dermatopathic lymphadenitis

For differentiation of follicular lymphoma from lymphocytoma cutis, see page 491

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Histopathology In the specific lesions of Hodgkin s disease two stages can be recognized Hodgkin s granuloma and Hodgkin s sar coma Hodgkin s sarcoma may follow Hodgkin s granuloma but the disease may show the morphology of Hodgkin s sarcoma at the onset (Jackson and Parker)

Hodgkin s granuloma is composed of a polymorphous infiltrate The majority of the constituent cells are the usual components of a chronic inflammatory infiltrate namely eosinophils neutrophils lymphocytes plasma cells histiocytes and fibroblasts In addition

from stem cells They occur as mononucleated and multinucleated cells The mononucleated Sternberg Reed giant cell possesses a very large irregularly shaped nucleus The multinucleated Sternberg Reed giant cell has either a double nucleus (mirror image nucleus) or several nuclei of dissimilar size and shape clustered in the center of the cell The nuclei of both mononucleated and multinucleated Sternberg Reed cells contain a prominent nucleolus and heavy clumps of chromatin Mitotic figures occur with moderate frequency in the stem cells reticulum cells and Sternberg Reed cells Hodgkin s granu loma has a tendency to focal necrosis and in lesions showing this phenomenon phagocytes are quite numerous Eosinophils are usually but not invariably present In some cases they constitute the pre dominant cell Collagen production is the result of the natural evolu tion of maturing histiocytes into fibroblasts Collagen production is scanty in the early phases and progresses steadily until broad fibrous septa separate the foci of cellularity into islands (Jackson and Parker)

Hodgkin s sarcoma differs from Hodgkin s granuloma by the pre ponderance of stem cells reticulum cells and Sternberg Reed cells

over all other elements comprising the tumor. Multinucleated cells and mitotic figures are numerous Fibrosis is absent or minimal Except for the presence of Sternberg-Reed cells, the histologic picture may greatly resemble that of stem-cell or reticulum cell lymphoma (Gall and Mallory)



Fig 266 Hodgkin's disease Low magnification There are two large masses of tumor cells In addition, numerous small collections of tumor cells are present throughout the dermis (×50)

The nodules and the tumors of the skin show large masses of cells in the dermis and not infrequently also in the subcutaneous fat (Fig 266) The histologic picture is more apt to be that of Hodgkin's granuloma than that of Hodgkin's sarcoma and is rarely as typical as in the lymph nodes The number of Sternberg Reed cells, on the presence of which the diagnosis depends, is often small and fibrosis

is less pronounced The presence of atypical reticulum cells with mitotic figures and of chronic inflammation may suggest mycosis fungoides Even then, however, a thorough search of serial sections will usually show a few Sternberg Reed giant cells (Fig 267) It is important not to confuse clumped reticulum or endothelial cells with multinucleated Sternberg Reed cells Reticulum and endothelial

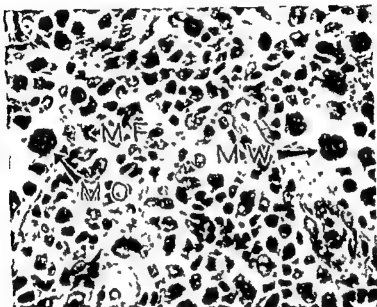


Fig 267 Hodgkin s disease High magnification of Figure 266 There is a dense polymorphous infiltrate It contains many atypical reticulum cells and several mitotic figures (M F) A mononucleated Sternberg Reed giant cell (M O) is present on the left a multinucleated Sternberg Reed giant cell (M W) on the right (×400)

cells have more regularly shaped paler staining nuclei than Sternberg Reed cells (Miller, Wrong)

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matit...

ease c... because Sternberg Reed cells frequently are absent In such instances, the histologic picture is either the same as in mycosis fungoides or shows merely a nonspecific chronic inflammatory infiltrate

The papular lesions show, as a rule, merely a nonspecific infiltrate of lymphocytes and histiocytes Occasionally, a few atypical reticulum cells with mitotic figures are present

over all other elements comprising the tumor Multinucleated cells and mitotic figures are numerous Fibrosis is absent or minimal Except for the presence of Sternberg Reed cells, the histologic picture may greatly resemble that of stem cell or reticulum cell lymphoma (Gall and Mallory)



FIG 266 Hodgkin s disease Low magnification There are two large masses of tumor cells In addition numerous small collections of tumor cells are present throughout the dermis (×50)

The nodules and the tumors of the skin show large masses of cells in the dermis and not infrequently also in the subcutaneous fat (Fig 266) The histologic picture is more apt to be that of Hodgkin s granuloma than that of Hodgkin s sarcoma and is rarely as typical as in the lymph nodes The number of Sternberg Reed cells, on the presence of which the diagnosis depends is often small and fibrosis

atrophicans vasculare (see page 305) develop either as a precursor or as a residuum of plaque like lesions

Histogenesis The histogenesis of mycosis fungoides is not solved fully Some authors explain the multiplicity of cell types as due to combined lymphoid and myeloid stimulation (Reimann Havens and Herbut) A most logical explanation is that first suggested by Fraser (1925 1936) He regarded mycosis fungoides as a form of reticulum cell lymphoma and believed that all other cells represented merely a defense reaction of the tissue against the tumor cells He pointed out that in the early stage of the disease the number of tumor cells is small and the inflammatory defense reaction pronounced As the disease advances the number of tumor cells increases while the defense reaction slackens until finally in the tumor stage the tumor cells proliferate uninhibitedly Fraser's theory finds support in the fact that also in other malignant diseases such as squamous-cell carcinoma and malignant melanoma an inflammatory tissue reaction tends to be present as long as the tumor cells are only moderately malignant but disappears as the malignancy of the tumor cells increases (see Squamous Cell Carcinoma page 330 and Malignant Melanoma page 460)

Histopathology The division of mycosis fungoides into three stages as described for the clinical picture pertains also to the histologic picture

In the first or erythematous stage the histologic picture not infrequently shows merely a banal inflammatory reaction so that a diagnosis of mycosis fungoides may be impossible In some instances however particularly if several specimens are taken for biopsy and serial sections are made areas may be found in which specific changes (described in the next paragraph) are present A finding which should always arouse one's suspicion of mycosis fungoides is the presence of patches of cellular infiltrate deeper in the dermis than one would expect to find them in a banal inflammatory infiltrate It must be emphasized that the decision whether or not early mycosis fungoides exists often is a very difficult one

In the second or plaque stage the histologic picture usually is diagnostic The following six changes may be present (1) great multiplicity of cell types (2) polymorphism of the [illegible]

of [illegible]

en [illegible]

de [illegible] abscesses

The variety of cells present includes *histiocytes* (= mature reticular cells) reticulum cells (= immature reticular cells) lymphocytes neutrophils eosinophils plasma cells and *fibroblasts* The number of

7. Mycosis Fungoides

Mycosis fungoides affects primarily and predominantly the skin In the late stage, however, the internal organs may show involvement (Berman; Post and Lincoln)

Several authors (Symmers; Gall and Mallory) have questioned the advisability of regarding mycosis fungoides as an entity Symmers has called mycosis fungoides a "clinical and pathologic nonexistent," and states that cases reported as mycosis fungoides represent histologically "either Hodgkin's disease, reticulum cell sarcoma or lymphosarcoma" It is true that some cases which clinically appear as mycosis fungoides prove, on histologic examination, to be one of the other types of lymphoma, and that cases which at the onset show the histologic picture of mycosis fungoides later assume the histologic characteristics of some other form of lymphoma Nevertheless mycosis fungoides has a distinct histologic picture which in the majority of cases remains as such throughout the disease and is found also in the internal lesions Transformation of one form of lymphoma into another occurs not only in mycosis fungoides but also in other forms of lymphoma This is evidence that all forms of lymphoma are related to each other but it does not obviate any classification

Clinically, as well as histologically, mycosis fungoides can be divided into three stages, the erythematous ("premycotic" or "prefungoid") stage, the plaque stage and the tumor stage All three stages may be present simultaneously and, occasionally tumors develop without the previous presence of erythematous or plaque lesions (mycosis fungoides d emblee) (Eller and Rein)

In the erythematous stage, the eruption may resemble eczema, psoriasis or parapsoriasis or have the appearance of generalized exfoliative dermatitis Most commonly one observes scattered erythematous, scaling patches of irregular outline They may be poorly demarcated or show a fairly sharp border Since such lesions often resemble eczema closely it is always advisable to consider the possibility of early mycosis fungoides when dealing with an atypical chronic eczematoid eruption Similarly in cases of generalized exfoliative dermatitis of unknown genesis the possibility of mycosis fungoides must always be borne in mind Itching is a prominent symptom in most instances of early mycosis fungoides

In the plaque stage circinate well defined, elevated plaques are seen They may show central clearing resulting in ringlike lesions

In the tumor stage, one observes round or lobulated, raised tumors of bluish to brownish red color They often undergo ulceration

In rare instances of mycosis fungoides, lesions of poikiloderma

vessel in their center If the patches are fairly large in size, they are strong evidence for lymphoma An almost pathognomonic finding occasionally encountered is the presence of so-called Pautrier ' micro-abscesses in the malpighian layer They consist of small accumula



Fig 269 Mycosis fungoides plaque stage High magnification of Figure 268 The infiltrate in the upper dermis shows marked multiplicity of cell types and polymorphism of the histiocytes Atypical reticulum cells with large hyperchromatic nuclei (mycosis cells ') are numerous There are several Pautrier micro-abscesses in the epidermis (×400)

tions of cells mainly lymphocytes and histiocytes (Fig 269) (It should be recalled that the Munro micro-abscesses of psoriasis are located in the horny layer and are composed of neutrophils) The epidermis in the plaque stage usually shows acanthosis with elongation of the rete ridges and may have an appearance similar to that found in psoriasis

In the third or tumor stage the infiltrate consists of large masses of cells and may occupy large areas of the dermis and even penetrate

eosinophils varies but often is considerable. Histiocytes are numerous. Staining for reticulum with Foot's stain will show, commensurate with the rather large number of histiocytes, a well-developed network of reticulum fibers. *The nuclei of the histiocytes vary greatly in size and shape.* In addition, their nuclei may show pyknosis (shrinking), karyorrhexis (breaking up into particles, "nuclear dust")



FIG. 268. Mycosis fungoides, plaque stage. Low magnification. The infiltrate in the upper dermis is diffuse, while in the lower dermis it consists of variously sized sharply demarcated patches. The epidermis contains several Pautrier micro-abscesses (P. A.) (×100)

and clumping. Immature and atypical reticulum cells, called mycosis cells, are present. Mycosis cells differ from histiocytes by having larger, more irregularly shaped and more deeply staining nuclei. Mitotic figures, *though not numerous, can, as a rule,* be found. (An occasional mitotic figure may occur in a banal inflammatory infiltrate, so that the *finding of one, two or even three mitotic* figures in a section does not necessarily mean mycosis fungoides.) The infiltrate in the plaque stage of mycosis fungoides is located largely *in the* upper dermis just as in a nonspecific chronic inflammation. Frequently, however, one finds, in addition, patches of cellular infiltrate in the lower dermis (Fig. 268). These patches usually have a blood

vessel in their center If the patches are fairly large in size, they are strong evidence for lymphoma An almost pathognomonic finding, occasionally encountered, is the presence of so-called Pautrier "micro abscesses in the malpighian layer They consist of small accumula



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In the third or tumor stage, the infiltrate consists of large masses of cells and may occupy large areas of the dermis and even penetrate

into the subcutaneous layer The pressure of the infiltrate may destroy the epidermis so that ulceration results The infiltrate still shows as a rule the same characteristics as in the plaque stage except that the number of mycosis cells and of mitotic figures is larger In some cases however the mycosis cells attain considerable size and may possess more than one nucleus so that they resemble mononu

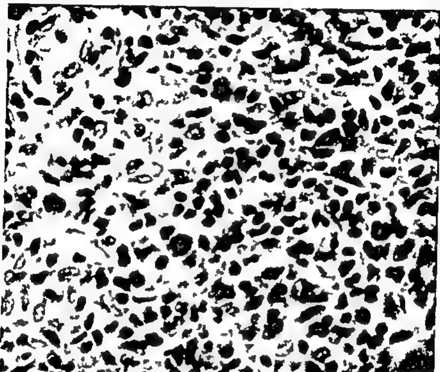


FIG 270 Mycosis fungoides tumor stage The infiltrate is polymorphous There are numerous mycosis cells Some of them are of considerable size and one located in the center has two nuclei These large mycosis cells resemble mononucleated or multinucleated Sternberg Reed cells (×400)

cleated or multinucleated *Sternberg Reed giant cells (Fig 270) If* such cells are conspicuous the infiltrate may be *identical with that* of Hodgkin s disease (Fraser and Schwartz Wile and Stiles) In other cases large immature reticulum cells like those seen in reticulum cell lymphoma may be present within the multicellular infiltrate (Fig 271) Occasionally immature reticulum cells are so numerous and inflammatory *cells so few that the infiltrate is identical* with that of reticulum cell lymphoma (Fraser and Schwartz)

The histologic appearance of generalized exfoliative dermatitis in mycosis fungoides may be that of either the erythematous or the plaque stage If it is that of the erythematous stage a diagnosis of mycosis fungoides may be *impossible (Montgomery)*

In poikiloderma atrophicans vasculare due to mycosis fungoides, the epidermis is atrophic and shows vacuolization of the cells of the basal layer A dense infiltrate lies in the upper dermis in close approximation to the epidermis and invades the epidermis in some areas The infiltrate may be that of either the erythematous or the plaque stage As a rule sufficient atypical cells are present to permit the diagnosis of mycosis fungoides (Oliver Hazel, Dostrovsky and

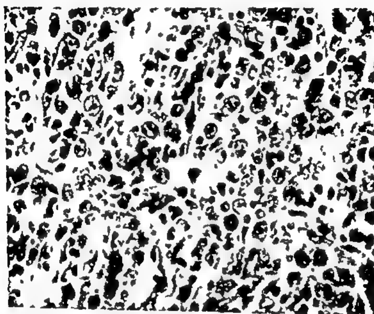


Fig 271 Mycosis fungoides tumor stage The polymorphous infiltrate contains many large immature reticulum cells like those seen in reticulum-cell lymphoma (×400)

Sagher) (For a discussion of poikiloderma atrophicans vasculare see page 305)

Involvement of Internal Organs The incidence of specific visceral lesions in mycosis fungoides is difficult to estimate from the literature Many reviews set the figure too high largely because the tendency exists in the dermatologic literature to regard a case of lymphoma as mycosis fungoides just because the primary or predominant lesions of the lymphoma are located on the skin It should be stressed that for a diagnosis of mycosis fungoides it is necessary that the majority of the cutaneous lesions either sho

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... many cases of lymphoma that

were not mycosis fungoides, in a review of autopsies recorded in the literature found visceral involvement in 51 out of 54 cases Cawley, Curtis and Leach, in their own material, found *visceral lesions in 8* out of 10 cases of supposed mycosis fungoides, but only 1 case showed the multiplicity of cell types *necessary for a diagnosis* of mycosis fungoides and that case had no visceral lesions It may be estimated that visceral lesions are found *on autopsy in* only about 20 per cent of the cases of mycosis fungoides, and usually they are not prominent or widespread.

When involvement of the internal organs is present in mycosis [illegible] cutaneous lesions (Ormsby and Finnerud) On the other hand, the visceral lesions, just as some of the cutaneous lesions, may be composed largely of immature reticulum cells and be indistinguishable from reticulum cell lymphoma (Fraser and Schwartz) or may present, due to the presence of Sternberg Reed giant cells the picture of Hodgkin's disease (Fraser, Wile and Stiles, Poulsen)

Of the various internal organs, the subcutaneous lymph nodes are affected most frequently However, the *infiltrate* in these lymph nodes is usually not that of mycosis fungoides but is nonspecific inflammatory, showing the histologic characteristics of dermatopathic lymphadenitis (see page 75) Nevertheless, the subcutaneous lymph nodes as well as the internal lymph nodes, the spleen the lungs, the liver, the kidneys, the gastro intestinal tract and many other organs may be involved by mycosis fungoides (Berman, Gates, Post and Lincoln) Involvement of the bone marrow however, has never been reported in true cases of mycosis fungoides (Poulsen) For this reason, mycosis fungoides *shows no significant* hemocytologic changes except that occasionally immature monocytes or lymphocytes are found in the blood In rare instances true lymphatic leukemia develops in the terminal *phase of the disease (Lane and Greenwood)*

Generalized Exfoliative Dermatitis in Lymphoma

Generalized exfoliative dermatitis is a fairly common occurrence in lymphoma *It occurs most commonly in* lymphocytic lymphoma Hodgkin's disease and mycosis fungoides but also in reticulum cell lymphoma, *particularly when accompanied* by monocytic leukemia Therefore, every case of persistent generalized exfoliative dermatitis *requires investigation* into the *possibility* of lymphoma According to Montgomery, 25 per cent of all cases of generalized exfoliative *dermatitis prove* to be associated with lymphoma The histologic picture of generalized exfoliative dermatitis in lymphoma may be,

in the early stage that of a nonspecific chronic inflammation In cases in which it is doubtful whether or not lymphoma exists thorough hemocytologic studies lymph node biopsy and sternal marrow biopsy are indicated and additional skin biopsies should be performed at intervals

Herpes Zoster in Lymphoma

The relatively frequent association of herpes zoster particularly of herpes zoster generalisatus with lymphoma is of interest Herpes zoster is most likely to occur in Hodgkin s disease and in lymphocytic lymphoma especially when lymphatic leukemia is present

Histopathology Histologic examination of the herpes zoster lesions may show the presence of a lymphomatous infiltrate (Barney Barton and O Leary) In addition autopsy may reveal lymphomatous cells in the intercostal nerve in the spinal ganglion in the nerve roots or in the cord segment corresponding to the site of the herpes zoster (Bluefarb) It may be assumed that the lymphomatous infiltrate produces a locus minoris resistentiae where the zoster virus localizes and multiplies

LYMPHOCYTOMA CUTIS (LYMPHADENOSIS BENIGNA CUTIS SPIEGLER FENDT SARCOID)

This condition occurs in two types a localized type (Loveman and Fliegelman Mopper and Rogin) and a disseminated type (Bafverstedt) In the localized type there is either a solitary nodule or a group of nodules in the disseminate type the lesions are scattered widely The face and the ear lobes are the sites of predilection The nodules are soft asymptomatic and radiosensitive Development into a lymphoma does not seem to occur

Histopathology A heavy infiltrate is present in the dermis usually separated from the epidermis by a narrow zone of normal collagen The infiltrate occasionally consists only of mature lymphocytes but in most cases there are also reticulum cells The two types of cells lie either intermingled with one another or in a follicular arrangement In the latter type of arrangement lymphocytes surround islands of reticulum cells resulting in structures resembling the follicles of lymph nodes (Fig 272) The lymphocytes and the reticulum cells are differentiated easily The lymphocytes have small round deeply staining nuclei lying closely packed because lymphocytes possess only little cytoplasm The reticulum cells have large irregularly shaped pale nuclei lying in loose arrangement bec

The nature of lymphocytoma cutis is not known. Although it suggests a lymphoma in its histologic architecture and is highly radiosensitive, it apparently is not a form of lymphoma. European authors (Hallam and Vickers; Hellier, Bafverstedt) have suggested that it represents a hyperplasia of pre-existing rudimentary lymphoid tissue.



Fig 272 Lymphocytoma cutis (lymphadenosis benigna cutis, Spiegler Fendt sarcoid). Low magnification. The infiltrate is composed of two types of cells lymphocytes, which lie in the dark staining areas, and reticulum cells, which lie in the light staining areas. At the right (L.F.), the arrangement of these cells resembles that encountered in a lymph follicle (×50)

Differential Diagnosis. The diagnosis is easily established in those cases of lymphocytoma cutis in which the infiltrate shows lymphocytes and reticulum cells in follicular arrangement. Even in cases in which the two cell types lie intermingled, the diagnosis usually can be made because the cells composing lymphocytoma, in contrast with those of reticulum cell lymphoma, are mature. Nevertheless, mistakes in diagnosis occur (Director and Kern). The greatest difficulties in diagnosis occur in those cases with a purely lymphocytic infiltrate because it may be impossible to rule out lymphocytic lymphoma. It is thus advisable always to make a diagnosis of lymphocytoma cutis with reservations, except in cases with obvious follicular formations (Loveman and Fliegelman).

Differentiation from follicular lymphoma (Brill Symmers disease) with which lymphocytoma cutis is not related is not difficult since in follicular lymphoma the follicular centers are larger more numerous and outlined more distinctly Also they are partially separated from the surrounding stroma by fissures which probably are the result of shrinkage of tissue during fixation Such fissures are not apt to occur in lymphocytoma cutis

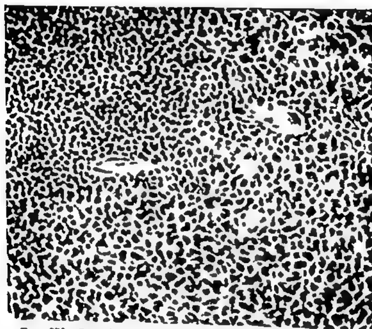


FIG 273 Lymphocytoma cutis (lymphadenosis benigna cutis Spiegler Fendt sarcoid) High magnification of Figure 272 Lymphocytes lie in the left upper half reticulum cells in the right lower half of the illustration (×200)

MYELOSIS

Myelosis is nearly always associated with leukemia in contrast with lymphoma in which leukemia is often absent The type of leukemia is myeloid leukemia On the other hand cutaneous lesions are less common in myelosis than in lymphoma Specific and nonspecific cutaneous lesions may occur however Just as in lymphoma there is no clearcut distinction between the two The two conditions merge imperceptibly and it is probable that most if not all of the nonspecific cutaneous manifestations result from tumor cells (Gates) (see page 472)

Clinically, the specific cutaneous lesions consist of from pinhead to walnut sized, firm nodules, which may coalesce into plaques and occasionally ulcerate The nonspecific cutaneous lesions (leukemids) may consist of macules, papules, pustules and purpuric lesions

Histopathology. Histologic examination of specific lesions shows the presence of dense masses of cells in the dermis and, occasionally, in the subcutaneous layer. Frequently, rows of cells extend from these masses into the surrounding tissue In addition, small groups of cells may be found scattered in the tissue spaces The majority of cells belong to the myeloid series, but lymphocytes and phagocytic histiocytes not infrequently are observed (Ketron and Gay) Some of the cells of the myeloid series are mature, but most are immature, being either myeloblasts or myelocytes They may be so immature that it is impossible to decide whether they belong to the myeloid or to the lymphoid reticular series of cells

Myeloblasts are about double the size of a mature polymorphonu clear leukocyte They possess a large, oval or round, pale staining nucleus and relatively little, nongranular cytoplasm They resemble lymphoblasts, although, as a rule, lymphoblasts have a coarser chro matin structure and less cytoplasm (Nekam) *Myelocytes* are about the same size as myeloblasts or slightly smaller They have, however, a smaller indented or lobate nucleus and abundant cytoplasm con taining granules which may be either fine neutrophilic or coarse eosinophilic Myeloblasts may or may not give a positive peroxidase reaction (also called oxidase reaction), while myelocytes always give a positive peroxidase reaction

The peroxidase reaction indicates the presence of the enzyme peroxidase, which occurs in mature and partly matured cells of the myeloid series but is absent in very immature cells of the myeloid series and in all cells of the lymphoid reticular series The peroxidase reaction is of great diagnostic value since it is positive in the majority of cases with myelosis and always negative in lymphoma Even very immature tumors of myelosis usually show at least a few areas in which the reaction is positive For the peroxidase reaction the speci men should be fixed in a 10 per cent formalin solution Frozen sec tions are used for staining On staining peroxidase positive cells show numerous black granules (Ketron and Gay)

Occasionally, the myeloid cells found in the cutaneous lesions are more immature than those in the bone marrow and the circulating blood This may be regarded as evidence that the cutaneous lesions in myelosis are autochthonous (Paul and Limarzi) It is probable that the myeloid cells form by myeloid transmutation of local reticular cells (Heller, Lewisohn and Palin)

CHLOROMA represents a rare form of myelosis in which the myelo blasts and the myelocytes show an unusual tendency to tumor forma tion The tumors are found most commonly in the bones especially the flat bones but may occur also in the skin The peroxidase re action is usually positive in the tumors The nature of the green pig ment present in the tumors is not yet fully known It represents an intermediary product in the breakdown of hemoglobin to bilirubin (Goodman and Iverson)

MONOCYTIC LEUKEMIA OF THE NAEGELI TYPE is a form of myeloid leukemia in contrast with monocytic leukemia of the Schilling type which is true monocytic leukemia In the Naegeli type the infiltrate in the cutaneous lesions is composed mainly of monocyte like cells so that differentiation from true (Schilling s) monocytic leukemia is not possible In the blood however myeloblasts and myelocytes are present in addition to monocyte like cells and the bone marrow shows myeloblastic hyperplasia without changes in the reticular cells (Watkins and Hall) While some regard monocytic leukemia of the Naegeli type as myeloid leukemia with a predominance of mono cytes most authors believe that the monocyte like cells differentiate from myeloblasts Montgomery and Watkins favor the latter view since they observed cells intermediate between myeloblasts and the monocyte like cells

EOSINOPHILIC LEUKEMIA a rare form of myeloid leukemia occa sionally has cutaneous lesions The cellular infiltrate present in the dermis may consist largely of immature primitive cells with but a few myelocytes and no eosinophils (Carmel Minno and Cook) or it may contain numerous eosinophils (Deme)

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Glossary

Acantholysis Loss of coherence between epidermal cells due to degeneration of the intercellular bridges It leads to the formation of clefts vesicles and bullae within the epidermis Occurs ... chronic pem

Acant

Alteration cavitaire See Intracellular Edema

Anaplasia Atypical de differentiation of cells occurring in malignant diseases Anaplastic cells have large hyperchromatic irregularly shaped nuclei and frequently show atypical mitotic figures

Ball

tion occurs in virus vesicles and is diagnostic of them See also Reticular Degeneration of Epidermal Cells

Bulla A cavity forming either within or beneath the epidermis and filled with lymph fluid A small bulla generally is called a vesicle and a slitlike bulla as seen in Darier s disease and senile keratosis a lacuna About the different modes of formation of bullae see the introduction to Chapter 7

Caseation necrosis A type of tissue death in which the affected area has lost its structural outline and consists of pale eosinophilic amorphous finely granular material Unless the necrosis is far advanced some pyknotic nuclei are still present No invasion of neutrophils occurs Caseation necrosis occurs especially in tuberculosis syphilis granuloma annulare and beryllium granuloma

Dyskeratosis Faulty keratinization of individual epidermal cells There are two types one occurring in benign diseases and the other in malignant diseases Benign dyskeratosis occurs in Darier s disease and occasionally in familial benign chronic pemphigus and consists of the formation of corps ronds and grains (see page 49) Malignant dyskeratosis occurs especially in Bowen s disease but also in squamous cell carcinoma and senile keratosis and consists of premature and atypical keratinization of individual cells

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Acanthosis Increase in thickness of the stratum malpighii

Altération cavitaire See Intracellular Edema

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Ballooning degeneration A type of degeneration of epidermal cells causing marked swelling with loss of the intercellular bridges Acantholysis results and a bulla forms Ballooning degeneration occurs in virus vesicles and is diagnostic of them See also Reticular Degeneration of Epidermal Cells

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Hydropic degeneration of basal cells: See "Liquefaction Degeneration of Basal Cells"

Hyperkeratosis: Excessive thickness of the horny layer. If caused by excessive formation of keratin, the granular layer is also thickened, as in lichen planus and lupus erythematosus If caused by retention of the horny layer, as in ichthyosis vulgaris, the granular layer is even smaller than normal

Incontinence of pigment: Loss of melanin from the cells of the basal layer due to damage to these cells with accumulation of the melanin in the upper dermis, inside as well as outside of melanophores It occurs in an idiopathic form in the disease called incontinentia pigmenti, and in a symptomatic form in lichen planus, lupus erythematosus, poikiloderma atrophicans vasculare, Riehl's melanosis and melanodermatitis toxica

Intercellular edema (spongiosis): Edema between squamous cells causing an increase in the width of the spaces separating them It occurs frequently in inflammatory processes of the skin especially in dermatitis eczema It does not cause formation of bullae or vesicles but contributes to their increase in size See also Intracellular Edema

Intracellular edema (altération cavitaire)· Edema within squamous cells If severe, it results in reticular degeneration (see below) of the affected cells and in the formation of multilocular bullae

Karyorrhexis: Fragmentation of nuclei

Liquefaction degeneration of basal cells A type of degeneration causing vacuolization and disintegration of basal cells It occurs in incontinentia pigmenti, lichen planus, lupus erythematosus, poikiloderma atrophicans vasculare, Riehl's melanosis, melanodermatitis toxica and lichen sclerosus et atrophicus with its variants kraurosis vulvae and balanitis xerotica obliterans In several of these diseases the liquefaction degeneration may cause incontinentia pigmenti (see above) In lichen planus lupus erythematosus and lichen sclerosus et atrophicus it may cause the formation of subepidermal bullae (see under Formation of Bullae introduction to Chapter 7)

Metachromasia· The phenomenon of reacting with a different color than that of the dye used for the staining Important examples of metachromasia occur in the staining of the granules of mast cells (see 'Urticaria Pigmentosa) and in the staining of mucin (see 'Myxedema) of amyloid (see "Amyloidosis) and of the fibrinoid material in fibrinoid degeneration (see "Acute Systemic Lupus Erythematosus) All four materials

stain purple with toluidine blue methylene blue thionine and cresyl violet Incidentally all four materials because of the presence of polysaccharides stain deeply red with the periodic acid Schiff reaction

Metaplasia Change of one type of tissue into another as it occurs for instance in the formation of bone in scars and in calcifying epithelioma (see Osteoma)

Micro-abscesses Small accumulations of cells in the epidermis Two types of micro abscesses occur the micro abscess of Munro in psoriasis and the micro abscess of Pautrier in mycosis fungoides For their description see those two diseases

Papilloma A tumor or tumor like proliferation of the skin characterized by papillomatosis (see below) and hyperkeratosis Five diseases show this type of proliferation nevus verrucosus (Jadassohn) keratosis senilis basal cell papilloma verruca vulgaris and acanthosis nigricans In typical instances histologic differentiation of these five diseases is easy but occasionally no more specific diagnosis than papilloma can be made

Papillomatosis Upward proliferation of papillae causing the surface of the epidermis to show irregular undulation

Parakeratosis Imperfec
nuclei in the horn
is absent in areas

Pyknosis Shrinking of nuclei

Reticular degeneration of epidermal cells A process in which severe intracellular edema causes bursting of epidermal cells and formation of a multilocular bulla The septa inside the bulla are formed by resisting cell walls Reticular degeneration plays a role in the formation of virus vesicles and those of contact dermatitis

Spongiform pustule of Kogoj A multilocular pustule located in the upper stratum malpighii and characterized by the presence of neutrophils inside of edematous epidermal cells The cellular walls of these epidermal cells traverse the pustule like the network of a sponge This type of pustule has a diagnostic appearance and occurs in acrodermatitis continua of Hallopeau impetigo herpetiformis keratosis blennorrhagica and Reiter s disease

Spongiosis See Intercellular Edema

Vesicle A small bulla (see Bulla) No sharp borderline can be drawn between a vesicle and a bulla Generally the term bulla is preferred in histopathology except for very small lesions that clinically are hardly visible

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Numerals in boldface type indicate the main reference to the subject

Villi Elongated and often tortuous papillae which are covered, as a rule, with but one or two layers of epidermal cells and extend into a vesicle a bulla or a cystic cavity Formation of villi is observed in Darier's disease, familial benign chronic pemphigus, pemphigus vulgaris, pemphigus vegetans syringo cystadenoma papilliferum and hidradenoma papilliferum

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